

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr **AMGEVITA**[®]
adalimumab injection

20 mg in 0.4 mL sterile solution (50 mg/mL), prefilled syringe for subcutaneous injection
40 mg in 0.8 mL sterile solution (50 mg/mL), prefilled syringe for subcutaneous injection
40 mg in 0.8 mL sterile solution (50 mg/mL), prefilled SureClick[®] autoinjector for subcutaneous injection

Professed Standard

Biologic Response Modifier

AMGEVITA (adalimumab) treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult and pediatric (13 to 17 years of age weighing \geq 40 kg) Crohn's disease, ulcerative colitis, adult and adolescent (12 to 17 years of age weighing \geq 30 kg) hidradenitis suppurativa, psoriasis or adult and pediatric uveitis, and familiar with the AMGEVITA efficacy and safety profile.

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TABLE OF CONTENTS

| | | |
|-----------|---|-----------|
| 1 | INDICATIONS | 5 |
| | 1.1 Pediatrics..... | 6 |
| | 1.2 Geriatrics..... | 7 |
| 2 | CONTRAINDICATIONS | 7 |
| 3 | SERIOUS WARNINGS AND PRECAUTIONS BOX | 8 |
| 4 | DOSAGE AND ADMINISTRATION | 9 |
| | 4.1 Dosing Considerations..... | 9 |
| | 4.2 Recommended Dose and Dosage Adjustment..... | 10 |
| | 4.3 Administration..... | 14 |
| | 4.4 Missed Dose..... | 14 |
| 5 | OVERDOSAGE | 14 |
| 6 | DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING | 14 |
| 7 | DESCRIPTION | 15 |
| 8 | WARNINGS AND PRECAUTIONS | 16 |
| | 8.1 Special Populations..... | 22 |
| | 8.1.1 Pregnant Women..... | 22 |
| | 8.1.2 Breast-feeding..... | 23 |
| | 8.1.3 Pediatrics..... | 23 |
| | 8.1.4 Geriatrics..... | 23 |
| 9 | ADVERSE REACTIONS | 23 |
| | 9.1 Adverse Reaction Overview..... | 23 |
| | 9.2 Clinical Trial Adverse Reactions..... | 30 |
| | 9.3 Less Common Clinical Trial Adverse Reactions..... | 47 |
| | 9.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data..... | 48 |
| | 9.5 Clinical Trial Adverse Reactions (Pediatrics)..... | 49 |
| | 9.6 Post-Market Adverse Reactions..... | 62 |
| 10 | DRUG INTERACTIONS | 63 |
| | 10.1 Serious Drug Interactions Box..... | 63 |
| | 10.2 Overview..... | 63 |
| | 10.3 Drug-Drug Interactions..... | 64 |
| | 10.4 Drug-Food Interactions..... | 65 |
| | 10.5 Drug-Herb Interactions..... | 65 |
| | 10.6 Drug-Laboratory Test Interactions..... | 65 |

| | | | |
|-----------|----------|--|-----------|
| | 10.7 | Drug-Lifestyle Interactions..... | 65 |
| 11 | | ACTION AND CLINICAL PHARMACOLOGY..... | 65 |
| | 11.1 | Mechanism of Action..... | 65 |
| | 11.2 | Pharmacodynamics..... | 65 |
| | 11.3 | Pharmacokinetics..... | 66 |
| | 11.4 | Special Populations and Conditions..... | 68 |
| 12 | | STORAGE, STABILITY AND DISPOSAL..... | 69 |
| 13 | | SPECIAL HANDLING INSTRUCTIONS..... | 69 |
| | | PART II: SCIENTIFIC INFORMATION..... | 71 |
| 14 | | PHARMACEUTICAL INFORMATION..... | 71 |
| 15 | | COMPARATIVE CLINICAL TRIALS..... | 72 |
| | 15.1 | Comparative Trial Design and Study Demographics..... | 72 |
| | 15.2 | Comparative Study Results..... | 73 |
| | 15.2.1 | Comparative Bioavailability Studies..... | 73 |
| | 15.2.1.1 | Pharmacokinetics..... | 73 |
| | 15.2.2 | Comparative Safety and Efficacy..... | 75 |
| | 15.2.2.1 | Efficacy..... | 75 |
| | 15.2.2.2 | Safety..... | 77 |
| | 15.2.2.3 | Immunogenicity..... | 77 |
| 16 | | COMPARATIVE NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY..... | 79 |
| | 16.1 | Comparative Non-Clinical Pharmacodynamics..... | 79 |
| | 16.2 | Comparative Toxicology..... | 80 |
| 17 | | CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG..... | 82 |
| | 17.1 | Adult..... | 82 |
| | 17.1.1 | Rheumatoid Arthritis..... | 82 |
| | 17.1.2 | Psoriatic Arthritis..... | 91 |
| | 17.1.3 | Ankylosing Spondylitis..... | 97 |
| | 17.1.4 | Crohn’s Disease..... | 99 |
| | 17.1.5 | Ulcerative Colitis..... | 106 |
| | 17.1.6 | Hidradenitis Suppurativa..... | 109 |
| | 17.1.7 | Psoriasis..... | 112 |
| | 17.1.8 | Uveitis..... | 117 |
| | 17.2 | Pediatric..... | 121 |
| | 17.2.1 | Polyarticular Juvenile Idiopathic Arthritis..... | 121 |
| | 17.2.2 | Pediatric Crohn’s Disease..... | 123 |

| | | |
|-----------|---|------------|
| 17.2.3 | Adolescent Hidradenitis Suppurativa | 125 |
| 17.2.4 | Pediatric Uveitis | 125 |
| 18 | NON-CLINICAL TOXICOLOGY – REFERENCE BIOLOGIC DRUG..... | 127 |
| 19 | SUPPORTING PRODUCT MONOGRAPHS | 132 |
| | PATIENT MEDICATION INFORMATION | 133 |
| | Single-Use Prefilled Syringe | 133 |
| | PATIENT MEDICATION INFORMATION | 149 |
| | Single-Use Prefilled Sureclick® Autoinjector | 149 |

AMGEVITA (adalimumab) (Amgen Canada Inc.) is a biosimilar biologic drug (biosimilar) to HUMIRA® (AbbVie Canada).

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Indications have been granted on the basis of similarity between AMGEVITA and the reference biologic drug HUMIRA®.

AMGEVITA treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult and pediatric (13 to 17 years of age weighing \geq 40 kg) Crohn's disease, ulcerative colitis, adult and adolescent (12 to 17 years of age weighing \geq 30 kg) hidradenitis suppurativa, psoriasis or adult and pediatric uveitis, and familiar with the AMGEVITA efficacy and safety profile.

AMGEVITA is indicated for:

Rheumatoid Arthritis

- reducing the signs and symptoms, inducing major clinical response and clinical remission, inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active rheumatoid arthritis (RA). AMGEVITA can be used alone or in combination with methotrexate (MTX) or other disease-modifying anti-rheumatic drugs (DMARDs).

When used as first-line treatment in recently diagnosed patients who have not been previously treated with MTX, AMGEVITA should be given in combination with MTX. AMGEVITA can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is contraindicated.

Polyarticular Juvenile Idiopathic Arthritis

- in combination with MTX, reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients, 2 years of age and older who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). AMGEVITA can be used as monotherapy in case of intolerance to MTX or when continued treatment with MTX is not appropriate (see **CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG, Pediatric, Polyarticular Juvenile Idiopathic Arthritis, Study Results [17.2.1]**). Adalimumab has not been studied in pediatric patients with polyarticular JIA aged less than 2 years.

Psoriatic Arthritis

- reducing the signs and symptoms of active arthritis and inhibiting the progression of structural damage and improving the physical function in adult psoriatic arthritis patients (PsA). AMGEVITA can be used in combination with MTX in patients who do not respond adequately to MTX alone.

Ankylosing Spondylitis

- reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS) who have had an inadequate response to conventional therapy.

Adult Crohn's Disease

- reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response to conventional therapy, including corticosteroids and/or immunosuppressants. AMGEVITA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Pediatric Crohn's Disease

- reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 13 to 17 years of age weighing ≥ 40 kg with severely active Crohn's disease and/or who have had an inadequate response or were intolerant to conventional therapy (a corticosteroid and/or aminosalicylate and/or an immunosuppressant) and/or a tumour necrosis factor (TNF) alpha antagonist.

Ulcerative Colitis

- treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy including corticosteroids, azathioprine and/or 6-mercaptopurine (6-MP) or who are intolerant to such therapies. The efficacy of AMGEVITA in patients who have lost response to or were intolerant to TNF-blockers has not been established.

Hidradenitis Suppurativa

- treatment of active moderate to severe hidradenitis suppurativa (HS) in adult and adolescent patients (12 to 17 years of age weighing ≥ 30 kg), who have not responded to conventional therapy (including systemic antibiotics).

Plaque Psoriasis

- treatment of adult patients with chronic moderate to severe plaque psoriasis (Ps) who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, AMGEVITA should be used after phototherapy has been shown to be ineffective or inappropriate.

Adult Uveitis

- treatment of non-infectious uveitis (intermediate, posterior and panuveitis) in adult patients with inadequate response to corticosteroids or as corticosteroid sparing treatment in corticosteroid-dependent patients.

Pediatric Uveitis

- treatment of chronic non-infectious anterior uveitis in pediatric patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

1.1 Pediatrics

Polyarticular Juvenile Idiopathic Arthritis

Adalimumab has not been studied in pediatric patients with polyarticular JIA less than 2 years of age or in pediatric patients with a weight below 10 kg.

Pediatric Crohn's Disease

The safety and efficacy of adalimumab, were investigated in pediatric patients 13 to 17 years of age weighing ≥ 40 kg with severely active Crohn's disease and/or who have had an inadequate response or were intolerant to conventional therapy (see **CLINICAL TRIALS, Pediatric Crohn's Disease [17.2.2]**).

Adolescent Hidradenitis Suppurativa

There are no clinical trials with adalimumab in adolescent patients with hidradenitis suppurativa. The dosage of adalimumab in these patients has been determined based on pharmacokinetic/ pharmacodynamic modeling and simulation (see **CLINICAL TRIALS, Pediatric, Adolescent Hidradenitis Suppurativa [17.2.3]**).

Pediatric Uveitis

Adalimumab has not been studied in pediatric patients with uveitis less than 2 years of age. Very limited data are available for pediatric patients with uveitis between 2 and < 3 years of age.

1.2 Geriatrics

Evidence from clinical studies and experience suggests that use of adalimumab in the geriatric population is not associated with differences in effectiveness. A brief discussion can be found under (**WARNINGS AND PRECAUTIONS, Geriatrics [8.1.4]**).

2 CONTRAINDICATIONS

- Patients with known hypersensitivity to AMGEVITA (adalimumab) or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING [6].
- Patients with severe infections such as sepsis, tuberculosis and opportunistic infections. (See **SERIOUS WARNINGS AND PRECAUTIONS BOX [3]**).
- Patients with moderate to severe heart failure (NYHA class III/IV). (See **WARNINGS AND PRECAUTIONS [8], Cardiovascular, Patients with Congestive Heart Failure**).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Hepatosplenic T-Cell Lymphoma

Very rare post-marketing reports of hepatosplenic T-cell lymphoma (HSTCL), a rare aggressive lymphoma that is often fatal, have been identified in patients treated with adalimumab. Most of the patients had prior infliximab therapy as well as concomitant azathioprine or 6-MP use for Crohn's disease. The potential risk with the combination of azathioprine or 6-MP and AMGEVITA should be carefully considered. The causal association of HSTCL with adalimumab is not clear.

Infections

Serious infections due to bacterial, mycobacterial, invasive fungal (disseminated or extrapulmonary histoplasmosis, aspergillosis, coccidioidomycosis), viral, parasitic, or other opportunistic infections have been reported in patients receiving tumour necrosis factor (TNF)-blocking agents. Sepsis, rare cases of tuberculosis, candidiasis, listeriosis, legionellosis and pneumocystis have also been reported with the use of TNF-blocking agents, including adalimumab. Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicemia. Hospitalization or fatal outcomes associated with infections have been reported. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to infections.

Treatment with AMGEVITA should not be initiated in patients with active infections, including chronic or localized infections, until infections are controlled. In patients who have been exposed to tuberculosis, and patients who have traveled in areas of high risk of tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, the risk and benefits of treatment with AMGEVITA should be considered prior to initiating therapy. (See **WARNINGS AND PRECAUTIONS [8], Infections, Other Opportunistic Infections**).

As with other TNF-blockers, patients should be monitored closely for infections (including tuberculosis) before, during and after treatment with AMGEVITA.

Patients who develop a new infection while undergoing treatment with AMGEVITA should be monitored closely and undergo a complete diagnostic evaluation. Administration of AMGEVITA should be discontinued if a patient develops a serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated.

Physicians should exercise caution when considering the use of AMGEVITA in patients with a history of recurrent infection or with underlying conditions which may predispose them to infections, or patients who have resided in regions where tuberculosis and histoplasmosis are endemic. (See **WARNINGS AND PRECAUTIONS [8], Infections, Tuberculosis**) and **(Adverse Drug Reaction Overview [9.1], Infections)**. The benefits and risks of treatment with AMGEVITA should be carefully considered before initiating therapy.

Pediatric Malignancy

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF-blockers, including adalimumab. (See **WARNINGS AND PRECAUTIONS [8], Malignancies, *Malignancies in Pediatric Patients and Young Adults***).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The needle cap on the prefilled syringe and needle cover on the prefilled autoinjector contains dry natural rubber (a derivative of latex) that may cause allergic reactions in individuals sensitive to latex.

Pediatrics

Polyarticular Juvenile Idiopathic Arthritis

See **Recommended Dosage and Dosage Adjustment [4.2], *Pediatrics*, Pediatric Juvenile Idiopathic Arthritis**.

Safety and effectiveness in pediatric patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg have not been established.

Pediatric Crohn's Disease

See **Recommended Dosage and Dosage Adjustment [4.2], *Pediatrics*, Pediatric Crohn's Disease**.

The majority (102/192) of pediatric patients with Crohn's disease studied were 13 to 17 years of age weighing \geq 40 kg in a clinical trial with adalimumab.

Adolescent Hidradenitis Suppurativa

See **Recommended Dosage and Dosage Adjustment [4.2], *Pediatrics*, Adolescent Hidradenitis Suppurativa**.

There are no clinical trials with adalimumab in adolescent patients with hidradenitis suppurativa. The dosage of adalimumab in these patients has been determined based on pharmacokinetic/pharmacodynamic modeling and simulation.

Pediatric Uveitis

See **Recommended Dosage and Dosage Adjustment [4.2], *Pediatrics*, Pediatric Uveitis**.

Safety and effectiveness in pediatric patients with uveitis less than 2 years of age have not been established. Very limited data are available for pediatric patients with uveitis between 2 and < 3 years of age.

Geriatrics

Evidence from clinical studies and experience suggests that use of adalimumab in the geriatric population is not associated with differences in effectiveness. No dose adjustment of AMGEVITA is needed for this population. A brief discussion can be found under (**WARNINGS AND PRECAUTIONS, Geriatrics [8.1.4]**).

Gender

No gender-related pharmacokinetic differences were observed after correction for a patient's body weight. Healthy volunteers and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics.

Race

No differences in immunoglobulin clearance would be expected among races. From limited data in non-Caucasians, no important kinetic differences were observed for adalimumab. Dosage adjustment is not required.

Hepatic Insufficiency

No pharmacokinetic data are available in patients with hepatic impairment. No dose recommendation can be made.

Renal Insufficiency

No pharmacokinetic data are available in patients with renal impairment. No dose recommendation can be made.

Disease States

Healthy volunteers and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics. (See **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions [11.4], Disease States**).

Concomitant Medications

MTX, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics or other DMARDs may be continued during treatment with AMGEVITA. When treated with adalimumab as monotherapy, some rheumatoid arthritis patients who experience a decrease in their response to adalimumab 40 mg every other week may benefit from an increase in dose intensity to adalimumab 40 mg every week.

4.2 Recommended Dose and Dosage Adjustment

Pediatrics

AMGEVITA is available as a 20 mg and 40 mg prefilled syringe and a 40 mg prefilled SureClick[®] autoinjector to administer a full 20 mg or 40 mg dose.

Polyarticular Juvenile Idiopathic Arthritis

The recommended dose of AMGEVITA for patients with polyarticular JIA from 2 years of age is based on body weight ([Table 1](#)). AMGEVITA is administered every other week via subcutaneous injection. AMGEVITA can be used in combination with MTX or as monotherapy in case of intolerance to MTX or when continued treatment with MTX is not appropriate.

Table 1 AMGEVITA Dose for Patients with Polyarticular Juvenile Idiopathic Arthritis

| Patient Weight | Dosing Regimen |
|------------------|------------------------|
| 10 kg to < 30 kg | 20 mg every other week |
| ≥ 30 kg | 40 mg every other week |

*A dose of 10 mg every other week can be considered for patients weighing 10 to < 15 kg.

Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Efficacy and safety in patients who do not respond by Week 16 have not been established.

There is no relevant use of adalimumab in children aged < 2 years in this indication.

Pediatric Crohn's Disease

The recommended AMGEVITA induction dose regimen for pediatric patients with severely active Crohn's disease and moderately active Crohn's disease with no response to conventional therapy is 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days), followed by 80 mg at Week 2 (given as two 40 mg injections in one day).

The recommended AMGEVITA maintenance dose regimen is 20 mg every other week beginning at Week 4.

For pediatric patients who experience a disease flare or non-response, dose escalation to 40 mg every other week may be considered (see **CLINICAL TRIALS [17.2.2]**).

The use of adalimumab in pediatric patients with Crohn's disease ages 13 to 17 has been evaluated up to one year in clinical studies.

If a patient has not responded by Week 12, continued therapy should be carefully reconsidered.

Adolescent Hidradenitis Suppurativa

The recommended AMGEVITA dose regimen for adolescent patients with hidradenitis suppurativa (12 to 17 years of age weighing ≥ 30 kg) is 80 mg at Week 0 followed by 40 mg every other week starting at Week 1 via subcutaneous injection.

In adolescent patients with inadequate response to AMGEVITA 40 mg every other week, an increase in dosing frequency to 40 mg every week may be considered. (See **CLINICAL TRIALS [17.2.3]**).

Antibiotics may be continued during treatment with AMGEVITA if necessary.

Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period.

Pediatric Uveitis

The recommended dose of AMGEVITA in combination with MTX for pediatric patients with chronic non-infectious anterior uveitis 2 years of age and older is based on body weight ([Table 2](#)). In pediatric uveitis, there is no experience in the treatment with adalimumab without concomitant treatment with MTX.

Table 2 AMGEVITA Dose for Pediatric Patients with Uveitis

| Patient Weight | Dosing Regimen |
|------------------|------------------------|
| 10 kg to < 30 kg | 20 mg every other week |
| ≥ 30 kg | 40 mg every other week |

When AMGEVITA is initiated in patients ≥ 6 years of age, an optional loading dose of 40 mg for patients < 30 kg or 80 mg for patients ≥ 30 kg may be administered one week prior to the start of maintenance therapy. No clinical data are available on the use of a loading dose for adalimumab in children < 6 years of age.

There are no data in the use of adalimumab in children aged less than 2 years for this indication.

Adults

Rheumatoid Arthritis

The recommended dose of AMGEVITA for adult patients with rheumatoid arthritis is 40 mg administered every other week as a subcutaneous injection.

Psoriatic Arthritis

The recommended dose of AMGEVITA for adult patients with psoriatic arthritis is 40 mg administered every other week as a subcutaneous injection.

For the rheumatoid arthritis and psoriatic arthritis indications, available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Ankylosing Spondylitis

The recommended dose of AMGEVITA for patients with ankylosing spondylitis is adalimumab 40 mg administered every other week via subcutaneous injection. Glucocorticoids, salicylates, NSAIDs, analgesics or DMARDs can be continued during treatment with AMGEVITA.

Crohn's Disease

The recommended AMGEVITA induction dose regimen for adult patients with Crohn's disease is 160 mg at Week 0 (dose can be administered as four subcutaneous injections in one day or as two subcutaneous injections per day for two consecutive days), followed by 80 mg at Week 2.

The recommended AMGEVITA maintenance dose regimen for adult patients with Crohn's disease is 40 mg every other week beginning at Week 4.

During treatment with AMGEVITA, other concomitant therapies (eg, corticosteroids and/or immunomodulatory agents) should be optimized.

For patients who experience a disease flare, dose escalation may be considered. See **(CLINICAL TRIALS [17.1.4])**.

Some patients who have not responded by Week 4 (induction period) may benefit from continued maintenance therapy through Week 12. Available data suggest that the clinical response is usually achieved at Week 4 of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

The use of adalimumab in Crohn's disease has been evaluated up to one year in controlled clinical studies. In open-label studies, 510/1,594 patients were evaluated for three years, and 118/1,594 patients for at least five years.

Ulcerative Colitis

The recommended AMGEVITA induction dose regimen for adult patients with ulcerative colitis is 160 mg at Week 0 (administered as four subcutaneous injections in one day or as two subcutaneous injections per day for two consecutive days), followed by 80 mg at Week 2. Beginning at Week 4, continue with a dose of 40 mg every other week. AMGEVITA should only be continued in patients who have responded during the first 8 weeks of therapy.

Aminosalicylates and/or corticosteroids may be continued during treatment with AMGEVITA. Azathioprine and 6-MP may be continued during treatment with AMGEVITA if necessary (see **SERIOUS WARNINGS AND PRECAUTIONS BOX [3]**).

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Hidradenitis Suppurativa

The recommended AMGEVITA initial dose for adult patients with hidradenitis suppurativa is 160 mg, followed by 80 mg two weeks later administered by subcutaneous injection. The first dose of 160 mg at Week 0 can be given in one day (four 40 mg injections) or split over two consecutive days (two 40 mg injections). The second dose of 80 mg at Week 2 is given as two 40 mg injections in one day.

The recommended AMGEVITA maintenance dose regimen for adult patients with hidradenitis suppurativa is 40 mg every week beginning four weeks after the initial dose.

Antibiotics may be continued during treatment with AMGEVITA if necessary.

In patients without any benefit after 12 weeks of treatment, continued therapy should be reconsidered.

Plaque Psoriasis

The recommended dose of AMGEVITA for adult patients with psoriasis is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week starting one week after the initial dose.

Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period.

Uveitis

The recommended dose of AMGEVITA for adult patients with non-infectious uveitis is an initial dose of 80 mg administered subcutaneously (two 40 mg injections), followed by 40 mg subcutaneously given every other week starting one week after the initial dose.

AMGEVITA can be initiated in combination with corticosteroids and/or other non-biologic immunomodulatory agents. Corticosteroids may be tapered in accordance with clinical practice starting two weeks after initiating treatment with AMGEVITA. There is limited experience with the initiation of treatment with adalimumab alone.

It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis.

4.3 Administration

AMGEVITA is intended for use under the guidance and supervision of a physician. A patient may self-inject AMGEVITA or a caregiver may inject AMGEVITA using either the AMGEVITA prefilled SureClick® autoinjector or prefilled syringe if a physician determines that it is appropriate, and with medical follow-up, as necessary, after proper training in subcutaneous injection technique.

You may leave AMGEVITA at room temperature for about 15 to 30 minutes before injecting. Do not remove the cap or cover while allowing it to reach room temperature. Carefully inspect the solution in the AMGEVITA prefilled SureClick® autoinjector or prefilled syringe for particulate matter and discoloration prior to subcutaneous administration. If particulates and discolorations are noted, do not use the product. AMGEVITA does not contain preservatives; therefore, discard unused portions of drug remaining from the syringe. NOTE: The needle cap on the prefilled syringe and on the prefilled autoinjector contains dry natural rubber (a derivative of latex) that may cause allergic reactions in individuals sensitive to latex.

Instruct patients using the AMGEVITA prefilled SureClick® autoinjector or prefilled syringe to inject the full amount contained in the syringe, according to the directions provided in the Instructions for Use (see **PART III: How to Take AMGEVITA**).

Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites and do not give injections into areas where the skin is tender, bruised, red or hard.

4.4 Missed Dose

Patients who miss a dose of AMGEVITA should be advised to inject this missed dose as soon as they become aware of it, and then follow with their next scheduled dose.

5 OVERDOSAGE

The maximum tolerated dose of AMGEVITA has not been established in humans. Multiple doses up to 10 mg/kg have been administered to patients in clinical trials with adalimumab without evidence of dose-limiting toxicities. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

| |
|---|
| For management of a suspected drug overdose, contact your regional poison control centre. |
|---|

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 3 Dosage Forms, Strengths, Composition and Packaging

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|--------------------------------|---|---|
| Subcutaneous injection | Single-use Prefilled Syringe, 20 mg, 40 mg Single-use Prefilled SureClick® Autoinjector, 40 mg | Latex (needle cap) For a complete listing of ingredients see text following this table |

Single-use Prefilled Syringe

Each single-use prefilled syringe contains: 20 mg or 40 mg adalimumab in a sterile, preservative-free solution containing 10 mM Glacial Acetic Acid, 0.10% (w/v) Polysorbate 80, Sodium Hydroxide for pH adjustment and 9.0% (w/v) Sucrose, in Water for Injection.

The prefilled syringe is composed of a 1 mL prefilled glass syringe with a fixed 27 or 29 gauge ½ inch needle.

AMGEVITA single-use prefilled syringes are available in 20 mg in 0.4 mL (50 mg/mL) and 40 mg in 0.8 mL (50 mg/mL) strengths.

AMGEVITA 20 mg in 0.4 mL (50 mg/mL) single-use prefilled syringes are supplied in a carton as a single-pack only with a single syringe. AMGEVITA 40 mg/0.8mL (50 mg/mL) single-use prefilled syringes are supplied in cartons as either a single-pack containing one syringe or as a two-pack containing two syringes.

Single-use Prefilled SureClick® Autoinjector

Each single-use prefilled autoinjector contains: 40 mg adalimumab in a sterile, preservative-free solution containing 10 mM Glacial Acetic Acid, 0.10% (w/v) Polysorbate 80, Sodium Hydroxide for pH adjustment and 9.0% (w/v) Sucrose, in Water for Injection.

The autoinjector is composed of a 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle.

AMGEVITA SureClick® autoinjectors are available in 40 mg in 0.8 mL (50 mg/mL) strength.

AMGEVITA 40 mg/0.8mL single-use prefilled SureClick® autoinjectors are supplied in cartons as either a single-pack containing one autoinjector or as a two-pack containing two autoinjectors.

7 DESCRIPTION

AMGEVITA is a recombinant human immunoglobulin (IgG1) monoclonal antibody that binds with high affinity and specificity to soluble tumour necrosis factor (TNF-alpha) but not lymphotoxin (TNF-beta). AMGEVITA is produced by recombinant DNA technology in a mammalian cell expression system. It consists of 2 heavy chains of the IgG1 subclass and 2 light chains of the human kappa subclass, which are covalently linked through disulfide bonds. It contains 1,330 amino acids and it has a molecular weight of approximately 148 kilodaltons.

8 WARNINGS AND PRECAUTIONS

Please see the **Serious Warnings and Precautions Box [3]** at the beginning of Part I: Health Professional Information.

General

Concurrent Administration of Biologic DMARDs or TNF-Antagonists

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent, etanercept, with no added benefit compared to etanercept alone. Because of the nature of the adverse events seen with the combination of etanercept and anakinra, similar toxicities may also result from the combination of anakinra and other TNF-blocking agents. Therefore, the combination of AMGEVITA and anakinra is not recommended. (See **Drug-Drug Interactions [10.3]**).

Concomitant administration of AMGEVITA with other biologic DMARDs (eg, anakinra and abatacept) or other TNF antagonists is not recommended based upon the increased risk for infections and other potential pharmacological interactions. (See **Drug-Drug Interactions [10.3]**).

Switching Between Biological DMARDs

When switching from one biologic to another, patients should continue to be monitored for signs of infection.

Surgery

There is limited safety experience of surgical procedures in patients treated with adalimumab. The long half-life of adalimumab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on AMGEVITA should be closely monitored for infections, and appropriate actions should be taken. There is limited safety experience in patients undergoing arthroplasty while receiving adalimumab.

Carcinogenesis and Mutagenesis

Long-term animal studies of adalimumab have not been conducted to evaluate the carcinogenic potential or its effect on fertility. No clastogenic or mutagenic effects of adalimumab were observed in the in vivo mouse micronucleus test or the Salmonella-Escherichia coli (Ames) assay, respectively. (See **NON-CLINICAL TOXICOLOGY [18], Mutagenicity and Carcinogenicity, In vitro Genotoxicity**).

Cardiovascular

Patients with Congestive Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF-blockers. Cases of worsening CHF have also been observed with adalimumab. Adalimumab has not been formally studied in patients with CHF; however, in clinical trials of another TNF-blocker, a higher rate of serious CHF-related adverse events was observed. Physicians should exercise caution when using AMGEVITA in patients who have heart failure and monitor them carefully. AMGEVITA is contraindicated in moderate to severe heart failure (see **CONTRAINDICATIONS [2]**).

Gastrointestinal

Small Bowel Obstruction

Failure to respond to treatment for Crohn's disease may indicate the presence of fixed fibrotic stricture that may require surgical treatment. Available data suggest that adalimumab does not worsen or cause strictures.

Hematologic Events

Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF-blocking agents. Adverse events of the hematologic system, including medically significant cytopenia (eg, thrombocytopenia, leukopenia) have been infrequently reported with adalimumab. The causal relationship of these reports to adalimumab remains unclear. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (eg, persistent fever, bruising, bleeding, pallor) while on AMGEVITA. Discontinuation of AMGEVITA therapy should be considered in patients with confirmed significant hematologic abnormalities.

Hypersensitivity Reactions

Allergic reactions (eg, allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed in approximately 1% of patients receiving adalimumab in clinical trials. (See **ADVERSE REACTIONS [9]**). Reports of serious allergic reactions, including anaphylaxis, have been received following adalimumab administration. If an anaphylactic reaction or other serious allergic reactions occur, administration of AMGEVITA should be discontinued immediately and appropriate therapy initiated.

Immune

Autoimmunity

Treatment with adalimumab may result in the formation of autoantibodies and rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with AMGEVITA, treatment should be discontinued. See (**Adverse Drug Reaction Overview [9.1], Autoantibodies**).

Immunosuppression

The possibility exists for TNF-blocking agents, including AMGEVITA, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 64 patients with rheumatoid arthritis who were treated with adalimumab, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T- and B-cells and NK-cells, monocyte/macrophages, and neutrophils. The impact of treatment with adalimumab on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood. (See **WARNINGS AND PRECAUTIONS [8], Infections and Malignancies**) and (**Adverse Drug Reaction Overview [9.1], Infections and Malignancies**).

Immunizations

In a randomized, double-blind, placebo-controlled study in 226 adult rheumatoid arthritis patients treated with adalimumab, antibody responses to concomitant pneumococcal and influenza vaccines were assessed. Protective antibody levels to the pneumococcal antigens were achieved by 86% of patients in adalimumab group compared to 82% in the placebo group. A total of 37% of adalimumab-treated patients and 40% of placebo-treated patients achieved at least a 2-fold increase in antibody titre to at least three out of five pneumococcal antigens. In the same study, 98% of patients in the adalimumab group and 95% in the placebo group

achieved protective antibody levels to the influenza antigens. A total of 52% of adalimumab-treated patients and 63% of placebo-treated patients achieved at least a 4-fold increase in antibody titer to at least two out of three influenza antigens.

It is recommended that pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating AMGEVITA therapy.

Patients on AMGEVITA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving adalimumab.

Administration of live vaccines to infants exposed to AMGEVITA in utero is not recommended for five months following the mother's last AMGEVITA injection during pregnancy. (See **Pregnant Women [8.1.1]**).

Infections

Tuberculosis

Tuberculosis, including reactivation and new onset of tuberculosis, has been reported in patients receiving adalimumab. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Before initiation, during and after treatment with AMGEVITA, patients should be evaluated for active and inactive ("latent") tuberculosis infection with a tuberculin skin test. Treatment of latent tuberculosis infections should be initiated prior to therapy with AMGEVITA. When tuberculin skin testing is performed for latent tuberculosis infection, an induration size of 5 mm or greater should be considered positive, even if vaccinated previously with Bacille Calmette-Guérin (BCG).

If active tuberculosis is diagnosed, AMGEVITA therapy must not be initiated.

The possibility of undetected latent tuberculosis should be considered, especially in patients who have immigrated from or traveled to countries with a high prevalence of tuberculosis or who had close contact with a person with active tuberculosis. If latent infection is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylactic treatment, in accordance with the Canadian Tuberculosis Standards and Centers for Disease Control and Prevention guidelines, before the initiation of AMGEVITA. Use of anti-tuberculosis prophylactic treatment should also be considered before the initiation of AMGEVITA in patients with several or significant risk factors for tuberculosis despite a negative test for tuberculosis and in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. The decision to initiate anti-tuberculosis therapy in these patients should only be made after taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy. If necessary, consultation should occur with a physician with expertise in the treatment of tuberculosis.

Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients receiving adalimumab. Also, active tuberculosis has developed in patients receiving adalimumab whose screening for latent tuberculosis infection was negative, and some patients who have been successfully treated for active tuberculosis have redeveloped active tuberculosis while being treated with TNF-blocking agents.

Patients receiving AMGEVITA should be monitored for signs and symptoms of active tuberculosis, particularly because tests for latent tuberculosis infection may be falsely negative. The risk of false negative tuberculin skin test results should be considered, especially in patients who are severely ill or immunocompromised. Patients should be instructed to seek medical advice if signs/symptoms suggestive of a tuberculosis infection (eg, persistent cough,

wasting/weight loss, low grade fever, listlessness) occur during or after therapy with AMGEVITA, and physicians should monitor for signs and symptoms of active tuberculosis, including patients who are tuberculosis skin test negative.

Other Opportunistic Infections

Opportunistic infections, including invasive fungal infections, have been observed in patients receiving adalimumab. These infections are not consistently recognized in patients taking TNF-blockers and this has resulted in delays in appropriate treatment, sometimes resulting in fatal outcomes.

Patients taking TNF-blockers are more susceptible to serious fungal infections such as histoplasmosis, coccidioidomycosis, blastomycosis, aspergillosis, candidiasis, and other opportunistic infections. Those who develop fever, malaise, weight loss, sweats, cough, dyspnea, and/or pulmonary infiltrates, or other serious systemic illness with or without concomitant shock should promptly seek medical attention for a diagnostic evaluation.

For patients who reside or travel in regions where mycoses are endemic, invasive fungal infections should be suspected if they develop the signs and symptoms of possible systemic fungal infection. Patients are at risk of histoplasmosis and other invasive fungal infections and hence clinicians should consider empiric antifungal treatment until the pathogen(s) are identified. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy. Patients who develop a severe fungal infection are also advised to stop the TNF-blocker until infections are controlled.

Hepatitis B Virus (HBV) Reactivation

Very rare cases of hepatitis B virus (HBV) reactivation have been associated with anti-TNF therapy. Clinically active HBV infection occurred following a latency period ranging from 3 to 20 months after initiation of therapy. In the majority of cases, patients were also taking other immunosuppressive drugs, including MTX, azathioprine, and/or corticosteroids. Hence, establishing a causal relationship to anti-TNF agents is confounded by the presence of these other medications. Where outcome information was provided, most patients were reported to have improved after antiviral treatment and/or discontinuation of the anti-TNF agent. However, fatal outcomes have also occurred in reported cases. Patients at risk of HBV infection should be evaluated for prior evidence of HBV infection before initiating anti-TNF therapy. Those identified as chronic carriers (i.e, surface antigen positive) should be monitored for signs and symptoms of active HBV infection throughout the course of therapy and for several months following discontinuation of therapy. Reactivation of HBV is not unique to anti-TNF-alpha agents and has been reported with other immunosuppressive drugs.

Malignancies

In the controlled portions of clinical trials of some TNF-blocking agents, including adalimumab, more cases of malignancies have been observed among patients receiving those TNF-blockers compared to control patients.

In the controlled and uncontrolled open-label portions of clinical trials of adalimumab, the more frequently observed malignancies, other than lymphoma and non-melanoma skin cancer, were breast, colon, prostate, lung, and melanoma.

Cases of acute and chronic leukemia have been reported in association with post-marketing TNF-blocker use in rheumatoid arthritis and other indications. Patients with rheumatoid arthritis

may be at a higher risk (up to 2-fold) than the general population for the development of leukemia, even in the absence of TNF-blocking therapy.

Malignancies in Pediatric Patients and Young Adults

Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF-blocking agents (i.e, including adalimumab). Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous post-marketing reports.

Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF-blockers including adalimumab. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF-blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with the immunosuppressants azathioprine or 6-MP concomitantly with a TNF-blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF-blocker or a TNF-blocker in combination with these other immunosuppressants. The potential risk with the combination of azathioprine or 6-MP and AMGEVITA should be carefully considered.

No malignancies were observed in the indicated pediatric patient population with Crohn's disease treated with adalimumab (n = 102) for 52 weeks in a clinical trial.

No malignancies were observed in pediatric patients aged 3 to 17 years with active JIA-associated chronic non-infectious anterior uveitis who were treated with adalimumab (n=90, randomized 2:1 to adalimumab:placebo) for up to 18 months in a clinical trial.

Treatment-emergent malignancies occurred in 2/480 adalimumab-treated ulcerative colitis patients in the double-blind controlled portion of two clinical trials (range of treatment duration from Weeks 0 to 52). The malignancies were squamous cell carcinoma and gastric cancer. Gastric cancer was considered serious and the patient discontinued as a result.

With current data it is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations.

Lymphoma

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving TNF-blockers compared to control patients.

However, for adalimumab, the occurrence of lymphoma was rare, and the follow-up period of placebo patients was shorter than for patients receiving TNF-antagonist therapy. The size of the control group and limited duration of the controlled portions of studies precludes the ability to draw firm conclusions. Furthermore, there is an increased background lymphoma risk in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which

complicates the risk estimation.

In combining the controlled and uncontrolled open-label portions of the 23 clinical trials in adult patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, psoriasis, and uveitis with a median duration of approximately 2.4 years, including 8764 patients and 27,196 patient-years of therapy, the observed rate of lymphomas (95% CI) is 1.2 [0.9, 1.7] per 1000 patient-years. This is approximately 3-fold higher than expected in the general population.

During the controlled and open-label periods of 14 trials with adalimumab, the overall standard incidence ratio (SIR) of malignancies was 0.99 [95% confidence interval (CI), 0.81 to 1.20]. With current knowledge in this area, a possible risk for development of lymphomas or other malignancies in patients treated with a TNF-antagonist cannot be excluded.

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving adalimumab. Additional caution should be exercised when considering AMGEVITA treatment in these patients.

Non-Lymphoma Malignancy

During the controlled portions of 21 adalimumab trials in adult patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, psoriasis and uveitis, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% CI) of 6.9 (4.4, 10.6) per 1,000 patient-years among 5196 adalimumab-treated patients versus a rate of 6.4 (3.5, 11.9) per 1,000 patient-years among 3,347 control patients (median duration of treatment of 4.0 months for adalimumab-treated patients and 3.9 months for control-treated patients).

During the controlled portions of 21 adalimumab trials in adult patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, psoriasis and uveitis, the rate (95% CI) of non-melanoma skin cancers was 8.9 (6.1, 13.1) per 1,000 patient-years among adalimumab-treated patients and 3.2 (1.3, 7.7) per 1,000 patient-years among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates (95% CI) of 2.7 (1.4, 5.5) per 1,000 patient-years among adalimumab-treated patients and 0.6 (0.1, 4.6) per 1,000 patient-years among control patients. The rate (95% CI) of lymphomas was 0.7 (0.2, 2.7) per 1,000 patient-years among adalimumab-treated patients and 0.6 (0.1, 4.6) per 1,000 patient-years among control patients.

The observed rate of malignancies, other than lymphoma and non-melanoma skin cancers, is approximately (95% CI) 8.5 (7.4, 9.7) per 1,000 patient years in the controlled portion of clinical trials and in ongoing and completed open-label extension studies. The observed rate of non-melanoma skin cancers is (95% CI) approximately 9.6 (8.5, 10.9) per 1,000 patient years, and the observed rate of lymphomas is (95% CI) approximately 1.3 (0.9, 1.8) per 1,000 patient years. The median duration of these studies is approximately 3.3 years and included 6276 adult patients who were on adalimumab for at least one year or who developed a malignancy within a year of starting therapy, representing over 26,044 patient years of therapy.

All patients, and in particular psoriasis patients with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of Psoralen Ultra-Violet A (PUVA) treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with AMGEVITA.

Neurologic Events

Use of TNF-blocking agents, including adalimumab, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating

disease, including multiple sclerosis, and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of AMGEVITA in patients with pre-existing or recent onset central nervous system demyelinating disorders; discontinuation of AMGEVITA should be considered if any of these disorders develop.

There is a known association between intermediate uveitis and central demyelinating disorders. Neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of AMGEVITA therapy to assess for pre-existing central demyelinating disorders.

8.1 Special Populations

8.1.1 Pregnant Women

The extent of exposure in pregnancy during clinical trials is very limited, consisting only of individual cases.

An embryo-fetal perinatal developmental toxicity study has been performed in cynomolgus monkeys at dosages up to 100 mg/kg (266 times human area under the curve (AUC) when given 40 mg adalimumab subcutaneously with MTX every week, or 373 times human AUC when given 40 mg adalimumab subcutaneously without MTX) and has revealed no evidence of harm to the fetuses due to adalimumab. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, AMGEVITA should be used during pregnancy only if clearly needed.

In a prospective cohort pregnancy exposure registry, conducted by the Organization of Teratology Information Specialists (OTIS)/MotherToBaby in the U.S. and Canada between 2004 and 2016, the risk of major birth defects in live-born infants was compared in 69 women with rheumatoid arthritis and 152 women with Crohn's disease treated with adalimumab at least during the first trimester with 74 women with rheumatoid arthritis and 32 women with Crohn's disease not treated with adalimumab during pregnancy. The proportion of major birth defects among live-born infants in the adalimumab-treated and untreated cohorts was 10% (8.7% rheumatoid arthritis, 10.5% Crohn's disease) and 7.5% (6.8% rheumatoid arthritis, 9.4% Crohn's disease), respectively.

No pattern of major birth defects was observed. This study cannot reliably establish whether there is an association between adalimumab and the risk for major birth defects because of methodological limitations of the registry, including small sample size, the voluntary nature of the study, and the non-randomized design.

Adalimumab may cross the placenta into the serum of infants born to women treated with AMGEVITA during pregnancy. Consequently, these infants may be at increased risk for infection. Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for five months following the mother's last AMGEVITA injection during pregnancy.

Labour and Delivery

There are no known effects of AMGEVITA on labour or delivery.

8.1.2 Breast-feeding

Limited information from case reports in the published literature indicates the presence of adalimumab in human milk at concentrations of 0.1% to 1% of the maternal serum level. Published data suggest that the systemic exposure of adalimumab to a breastfed infant is expected to be low because adalimumab is a large molecule and is degraded in the gastrointestinal tract. However, the effects of local exposure in the gastrointestinal tract are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for adalimumab and any potential adverse effects on the breastfed child from adalimumab or from the underlying maternal condition.

8.1.3 Pediatrics

Polyarticular Juvenile Idiopathic Arthritis

The efficacy and safety of adalimumab have been studied in pediatric patients aged 4 to 17 years (n = 171) and 2 to 4 years (n = 32). No overall differences were observed in the efficacy and safety between the two age groups. Adalimumab has not been studied in pediatric patients with polyarticular JIA less than 2 years of age or in pediatric patients with a weight below 10 kg.

Pediatric Crohn's Disease

The majority (102/192) of pediatric patients with Crohn's disease studied were 13 to 17 years of age weighing \geq 40 kg.

Pediatric Uveitis

The efficacy and safety of adalimumab have been studied in pediatric patients with uveitis aged 2 to 17 years (n=90, randomized 2:1 to adalimumab:placebo). Very limited data are available for pediatric patients with uveitis between 2 and < 3 years of age. Serious adverse events were more frequent in children 4 years of age and younger

8.1.4 Geriatrics

A total of 519 rheumatoid arthritis patients 65 years of age and older, including 107 patients 75 years and older, received adalimumab in clinical Studies DE009, DE011, DE019 and DE031. No overall differences in effectiveness were observed between these patients and younger patients. The frequency of serious infection and malignancy among adalimumab-treated patients over age 65 was higher than for those under the age of 65. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

9 ADVERSE REACTIONS

The adverse drug reaction profiles reported in clinical studies that compared AMGEVITA to the reference biologic drug were comparable. The description of adverse reactions in this section is based on clinical experience with the reference biologic drug.

9.1 Adverse Reaction Overview

The most serious adverse reactions were (see **WARNINGS AND PRECAUTIONS [8]**):

- serious infections
- neurologic events

- malignancies

The most common adverse reaction in rheumatoid arthritis patients treated with adalimumab, was injection site reactions. In controlled trials for rheumatoid arthritis, polyarticular JIA, psoriatic arthritis, ankylosing spondylitis, adult and pediatric Crohn's disease, ulcerative colitis, adult hidradenitis suppurativa, psoriasis and adult uveitis, 13% of patients treated with adalimumab developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 7% of patients receiving control treatment. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of rheumatoid arthritis patients who discontinued treatment due to adverse events during the double-blind, placebo-controlled portion of rheumatoid arthritis Studies DE009, DE011, DE019 and DE031 was 7.0% for patients taking adalimumab, and 4.0% for placebo-treated patients. The most common adverse events leading to discontinuation of adalimumab were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Among patients with rheumatoid arthritis in placebo-controlled studies, deaths occurred in 8 of 1,380 (0.58%) adalimumab-treated patients compared to 1 of 690 (0.14%) placebo-treated patients. The rate of deaths in both treatment arms is less than expected in the normal population with a standard mortality ratio (SMR) of 0.87 (95% CI, 0.38, 1.72) in the adalimumab group and 0.25 (95% CI, 0.00, 1.37) in the placebo group.

In Study DE019, 553 patients were exposed to at least one dose of adalimumab and 202 patients completed 10 years of study. A total of 24 patients died during the 10-year exposure period to adalimumab (4 during the double-blind phase, 14 during the open-label extension phase and an additional 6 after study drug termination). Among the treatment-emergent deaths, the most common reasons were: 4 sepsis, 3 cancers and 3 respiratory system events. However, the total number of deaths was not higher than that calculated according to age-adjusted Standardized Mortality Rates.

Of the 553 patients, 23.0% discontinued due to an adverse event. The most common adverse events associated with discontinuation of study drug were pneumonia and breast cancer (n = 5 each). Fatigue, pneumonia, cellulitis, and histoplasmosis (n = 3 each) were the most common treatment-related adverse events leading to discontinuation of study drug.

In total, 49% of patients treated with adalimumab experienced a serious adverse event; 15.7% were considered at least possibly related to study drug. The most common serious adverse events were rheumatoid arthritis disease flare (n = 35, 6.3%), pneumonia (n = 26, 4.7%) and myocardial infarction (n = 10, 1.8%); of these, only pneumonia was considered to be at least possibly related to study drug.

The most frequently reported treatment-emergent adverse events were infections (total n = 448, 81%; serious n = 85, 15.4%) and injection site reactions (n = 115, 20.8%).

Adverse events of special interest among the 553 patients included 35 patients with malignancies other than non-melanoma skin cancer (including 5 cases of lymphoma); and 3 patients with tuberculosis. Serious adverse events of special interest included 5 patients each with pulmonary embolism and diverticulitis; 2 patients with multiple sclerosis; and 1 patient with hypersensitivity reaction.

Adalimumab has also been studied in 542 patients with early rheumatoid arthritis (disease duration less than three years) who were MTX naïve (Study DE013). No new safety signals were seen in this patient population compared to the safety profile seen in adalimumab Studies DE009, DE011, DE019 and DE031. In this study, deaths occurred in 5 of 542 (0.92%) adalimumab-treated patients compared to 1 of 257 (0.39%) MTX-treated patients. The rate of

deaths in both treatment arms is less than expected in the normal population with a SMR of 0.57 (95% CI, 0.18, 1.32) in the adalimumab group and 0.22 (95% CI, 0.00, 1.23) in the MTX group.

Adalimumab has also been studied in 395 patients with psoriatic arthritis in two placebo-controlled studies and in an open-label extension study, in 393 patients with ankylosing spondylitis in two placebo-controlled studies and in over 1,500 patients with Crohn's disease in five placebo-controlled and two open-label extension studies. The safety profile for patients with psoriatic arthritis treated with adalimumab 40 mg every other week was similar to the safety profile seen in patients with rheumatoid arthritis, adalimumab Studies DE009, DE011, DE019, DE031 and DE013. During the controlled period of the psoriatic arthritis studies, no deaths occurred in the adalimumab-treated or placebo-treated patients. During the psoriatic arthritis open-label study, two deaths occurred in 382 patients with 795.7 patient-years of exposure. The rate of deaths is less than expected in the normal population with a SMR of 0.39 (95% CI, 0.04, 1.43). Among patients enrolled in the psoriasis open-label study, 5 deaths occurred in 1,468 patients with 4,068.6 patient-years of exposure.

Adalimumab has also been studied in 1,010 patients with ulcerative colitis in two randomized, double-blind, placebo-controlled studies (M06-826, 8 weeks and M06-827, 52 weeks) and an open-label extension study. No new safety signals were seen in the ulcerative colitis patient population. During the controlled period of the ulcerative colitis studies, no deaths occurred in the adalimumab-treated or placebo-treated patients. In the overall adalimumab ulcerative colitis development program of 1,010 patients with 2007.4 patient years of exposure (622 patients were treated for >1 year), 2 treatment-emergent deaths occurred during the long-term open-label extension study (cardio-respiratory arrest and right ventricular failure). There were no new safety signals compared to the known safety profile of adalimumab in the double-blind controlled portion of ulcerative colitis studies.

Adalimumab has also been studied in 727 adult patients with hidradenitis suppurativa in three randomized, double-blind, placebo-controlled studies and an open-label extension study. No deaths were reported during the placebo-control periods. In the overall adalimumab hidradenitis suppurativa development program of 727 patients with 635.7 patient years of exposure (281 patients were treated for >1 year), 2 treatment-emergent deaths occurred (cardio-respiratory arrest and autoimmune pancreatitis). No new safety signals were seen in the hidradenitis suppurativa adult patient population.

Adalimumab has also been studied in 464 adult patients with uveitis in two randomized, double-masked, placebo-controlled studies (M10-877 and M10-880) and an open-label extension study (M11-327). No new safety signals for adalimumab were identified in the uveitis adult patient population. In the overall adalimumab adult uveitis development program of 464 adalimumab adult patients with 1308.2 patient-years of exposure, 6 treatment-emergent deaths were reported (chronic renal failure, aortic dissection/acute tamponade, B-cell lymphoma, brain abscess, pancreatic carcinoma and accident). Two deaths occurred during the controlled period of the uveitis adult studies and 4 during the ongoing open-label extension study.

Autoantibodies

Patients treated with adalimumab, had serum samples tested for autoantibodies at multiple time points in Studies DE009, DE011, DE019, DE031 and DE013. In those rheumatoid arthritis controlled trials, 11.9% of patients treated with adalimumab and 8.1% of placebo- or active control-treated patients who had negative baseline antinuclear antibody titres, developed positive titres at Week 24. Two patients out of 3441 treated with adalimumab developed clinical signs suggestive of new onset lupus-like syndrome. The patients improved following

discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with adalimumab on the development of autoimmune diseases is unknown.

Immunogenicity

In patients treated with adalimumab, formation of anti-adalimumab antibodies is associated with increased clearance and reduced efficacy of adalimumab. There is no apparent correlation between the presence of anti-adalimumab antibodies and adverse events.

Pediatric

In clinical trials with adalimumab therapy for polyarticular JIA, the proportion of patients achieving PedACR response was lower in anti-adalimumab antibody-positive patients compared with anti-adalimumab antibody-negative patients.

In patients with polyarticular JIA who were 4 to 17 years (Study DE038), anti-adalimumab antibodies were identified in 27/171 subjects (15.8%) treated with adalimumab. In patients not given concomitant MTX, the incidence was 22/86 (25.6%), compared to 5/85 (5.9%) when adalimumab was used as add-on to MTX. In patients with polyarticular JIA who were 2 to <4 years of age or 4 years of age and older weighing < 15 kg (Study M10-444), anti-adalimumab antibodies were identified in 7% (1/15) of patients, and the one patient was receiving concomitant MTX.

In patients 13 to 17 years of age with severely active Crohn's disease, anti-adalimumab antibodies were identified in 3.5% (4/114) of patients receiving adalimumab.

Adult

Rheumatoid arthritis patients in Studies DE009, DE011, and DE019 were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58/1062) of adult rheumatoid arthritis patients receiving adalimumab developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing in vitro. Patients treated with concomitant MTX had a lower rate of antibody development than patients on adalimumab monotherapy (1% versus 12%). With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the American College of Rheumatology (ACR 20) response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of adalimumab is unknown.

In patients with psoriatic arthritis, anti-adalimumab antibodies were identified in 38/376 patients (10%) treated with adalimumab. In patients not given concomitant MTX, the incidence was 13.5% (24/178 patients), compared to 7% (14/198 patients) when adalimumab was used as add-on to MTX.

In patients with ankylosing spondylitis, anti-adalimumab antibodies were identified in 17/204 patients (8.3%) treated with adalimumab. In patients not given concomitant MTX, the incidence was 16/185 (8.6%), compared to 1/19 (5.3%) when adalimumab was used as add-on to MTX.

In patients with Crohn's disease, anti-adalimumab antibodies were identified in 2.6% (7/269) of patients receiving adalimumab.

In patients with ulcerative colitis, anti-adalimumab antibodies were identified in 5.0% (19/379) of patients receiving adalimumab. The clinical significance of this is unknown.

In patients with moderate to severe hidradenitis suppurativa, anti-adalimumab antibodies were identified in 10/99 patients (10.1%) treated with adalimumab.

In patients with psoriasis, anti-adalimumab antibodies were identified in 77/920 patients (8.4%) treated with adalimumab monotherapy.

In patients with plaque psoriasis, the rate of antibody development with adalimumab monotherapy was 8%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among these patients whose serum adalimumab levels were < 2 mcg/mL (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In patients with plaque psoriasis on long-term adalimumab monotherapy who participated in a withdrawal and retreatment study and whose serum adalimumab levels were < 2 mcg/mL (approximately 12% of total patients studied), the immunogenicity rate was 16%; the overall rate of antibody development prior to withdrawal was 1.9%, and 2.3% after retreatment.

In patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 23% of total patients studied), the immunogenicity rate was 21.1%.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab in an enzyme-linked immunosorbent assay (ELISA), and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Infections

Adults

In 23 controlled trials for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, psoriasis and uveitis, the rate of infection was 147.4 per 100 patient-years in 5630 adalimumab-treated patients and 142.7 per 100 patient-years in 3587 control-treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, and sinusitis. Most patients continued on adalimumab after the infection resolved.

The incidence of serious infections was 3.4 per 100 patient-years in adalimumab-treated patients and 3.2 per 100 patient-years in placebo and active control-treated patients.

In controlled and open-label studies with adalimumab, serious infections such as legionellosis (0.02 per 100 patient-years) have been reported. No cases of listeriosis have been reported and therefore, an estimated rate of 0.01 per 100 patient-years was calculated. Both infections have been reported spontaneously during the post-marketing period.

In controlled and open-label studies with adalimumab, serious infections (including fatal infections, which occurred rarely) have been reported, which include reports of tuberculosis (including miliary and extra-pulmonary locations) and invasive opportunistic infections (eg, disseminated histoplasmosis, pneumocystis carinii pneumonia, and aspergillosis). Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease.

In the double-blind controlled portion of two clinical trials with adalimumab in patients with ulcerative colitis, serious infections occurred in 4/480 patients treated with adalimumab; they were appendicitis (n = 1), anal abscess (n = 1), catheter sepsis (n = 1) and salmonellosis (n = 1). Serious infections occurred in 8 placebo patients. Opportunistic infections occurred in 7/480 patients treated with adalimumab; they were candidiasis (n = 3), esophageal candidiasis (n = 1) and oral candidiasis (n = 3). Opportunistic infections occurred in 3 placebo patients.

In the double-blind controlled portion of three clinical trials with adalimumab in patients with hidradenitis suppurativa, serious infections occurred in 4/419 patients treated with adalimumab; they were Escherichia infection (n = 1), genital infection bacterial (n = 1), infection (n = 1), pilonidal cyst (n = 1) and pyelonephritis (n = 1). Serious infections occurred in 2/366 placebo patients.

In the double-masked controlled portion of two clinical trials with adalimumab in patients with uveitis, serious infections occurred in 7/250 (2.8%) patients treated with adalimumab; they were pneumonia (n = 2), and 1 each of bronchitis, pilonidal cyst, pneumonia Legionella, tuberculosis, upper respiratory tract infection and urinary tract infection. Serious infections occurred in 4/250 (1.6%) placebo patients. Opportunistic infections occurred in 7/250 patients treated with adalimumab; they were active tuberculosis (n = 1), latent tuberculosis (n = 4) and oral candidiasis (n = 2). Latent tuberculosis occurred in 1 placebo-treated patient. In the open-label extension study (M11-327), the exposure adjusted incidence rate of serious infections was increased in patients who received concomitant systemic corticosteroids and immunosuppressants in addition to treatment with adalimumab.

Pediatrics

In a controlled trial for polyarticular JIA (Study DE038), the rate of adverse events of infections was 238.5 per 100 patient-years in the adalimumab-treated JIA patients compared to 269.5 per 100 patient-years in control (placebo) treated patients, and the rate of serious infections was 6.1 per 100 patient-years in the adalimumab-treated JIA patients compared to 0 events in control (placebo) treated patients.

In an open-label trial for polyarticular JIA (Study M10-444), the rate of adverse events of infections was 206.2 per 100 patient-years while receiving adalimumab and the rate of serious infections was 6.7 per 100 patient-years while receiving adalimumab.

In a randomized double-blind trial (M06-806) for the indicated pediatric patient population with Crohn's disease, the rate of infections was 161.4 per 100 patient-years for the High-Dose group and 225.9 per 100 patient-years for the Low-Dose group. The rates of serious infections were 9.5 per 100 patient-years for the High-Dose group and 3.7 per 100 patient-years for the Low-Dose group. The rates of infections were 55.8% (29/52) and 52.0% (26/50) for High-Dose and Low-Dose groups, respectively. The rates of serious infections were 5.8% (3/52) and 2.0% (1/50) for High-Dose and Low-Dose groups, respectively and included anal abscess, gastroenteritis, and histoplasmosis disseminated in the High-Dose group and Bartholin's abscess in the Low-Dose group.

In a randomized controlled trial (SYCAMORE) for pediatric patients with active JIA-associated chronic non-infectious anterior uveitis, the rate of adverse events of infections was 236.4 per 100 patient-years (77%) for the adalimumab-treated group compared to 164.5 per 100 patient-years (40%) for the control (placebo) group. The rate of serious infections was 17.1 per 100 patient-years (13%) in the adalimumab-treated uveitis patients compared to 0 events in control (placebo) treated patients.

Injection Site Reactions

In controlled trials in adults and children, 13% of patients treated with adalimumab developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 7% of patients receiving placebo or active control. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

Malignancies

More cases of malignancy have been observed in adalimumab-treated patients compared to control-treated patients in clinical trials. (See **WARNINGS AND PRECAUTIONS [8], Malignancies**).

Neurologic Events

In 21 controlled trials for adult patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, and psoriasis, the rate of new onset or exacerbation of central nervous system demyelinating disease (including multiple sclerosis and optic neuritis) and peripheral demyelinating disease (including Guillain-Barre syndrome) was less than 0.4 per 1000 patient-years in 5,380 adalimumab-treated patients and 0.7 per 1000 patient-years in 3,337 control-treated patients. In controlled and open-label studies for adult patients treated with adalimumab, the rate (95% CI) of demyelinating diseases was 0.7 (0.4, 1.1) per 1000 patient-years. Demyelinating diseases were reported spontaneously during the post-marketing period.

In the double-masked controlled portion of two clinical trials with adalimumab in adult patients with adult uveitis, 1 (0.4%) case of multiple sclerosis was reported in 250 patients treated with adalimumab. In the uveitis development program including the open-label study, the rate (95% CI) of demyelinating diseases (i.e, multiple sclerosis and optic neuritis) was 5.4 (2.2, 11.0) per 1000 patient-years.

(See **WARNINGS AND PRECAUTIONS [8], Neurologic Events**).

Psoriasis: New Onset and Worsening

Cases of new onset psoriasis, including pustular psoriasis and palmoplantar psoriasis, and cases of worsening of pre-existing psoriasis have been reported with the use of TNF-blockers, including adalimumab. Many of these patients were taking concomitant immunosuppressants (eg, MTX, corticosteroids). Some of these patients required hospitalization. Most patients had improvement of their psoriasis following discontinuation of their TNF-blocker. Some patients have had recurrences of the psoriasis when they were re-challenged with a different TNF-blocker. Discontinuation of AMGEVITA should be considered for severe cases and those that do not improve or that worsen despite topical treatments.

Liver Enzyme Elevations

In controlled Phase 3 trials of adalimumab (40 mg subcutaneous every other week), in patients with rheumatoid arthritis and psoriatic arthritis with a control period duration ranging from 4 to 104 weeks, alanine aminotransferase (ALT) elevations ≥ 3 x upper limit of normal (ULN) occurred in 3.7% of adalimumab-treated patients and 1.6% of control-treated patients. Since many of the patients in these trials were also taking medications that cause liver enzyme elevations (eg, NSAIDs, MTX), the relationship between adalimumab and the liver enzyme elevations is not clear.

In controlled Phase 3 trials of adalimumab (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week), in adult patients with Crohn's disease with a control period duration ranging from 4 to 52 weeks, ALT elevations $\geq 3 \times$ ULN occurred in 0.9% of adalimumab-treated patients and 0.9% of control-treated patients.

In controlled Phase 3 trials of adalimumab (initial doses of 160 mg and 80 mg on Days 1 and 15, respectively, followed by 40 mg every other week), in patients with ulcerative colitis with a control period duration ranging from 1 to 52 weeks, ALT elevations $\geq 3 \times$ ULN occurred in 1.5% of adalimumab-treated patients and 1.0% of control-treated patients. The incidence of ALT elevations $\geq 5 \times$ ULN was 0.5% in adalimumab-treated patients and 0.2% in control-treated patients.

In controlled Phase 3 trials of adalimumab (initial dose of 80 mg then 40 mg every other week), in patients with plaque psoriasis with a control period duration ranging from 12 to 24 weeks, ALT elevations $\geq 3 \times$ ULN occurred in 1.8% of adalimumab-treated patients and 1.8% of control-treated patients.

In controlled Phase 3 trials of adalimumab (40 mg every other week), in patients with ankylosing spondylitis with a control period of 12 to 24 weeks, ALT elevations $\geq 3 \times$ ULN occurred in 2.4% of adalimumab-treated patients and 0.7% of control-treated patients.

In controlled trials of adalimumab (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in adult patients with hidradenitis suppurativa with a control period duration ranging from 12 to 16 weeks, ALT elevations $\geq 3 \times$ ULN occurred in 0.3% of adalimumab-treated patients and 0.6% of control-treated patients.

In controlled Phase 3 trials of adalimumab (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in patients with adult uveitis with an exposure of 165.4 patient-years and 119.8 patient-years in adalimumab-treated and control-treated patients, respectively, ALT elevations $\geq 3 \times$ ULN occurred in 2.4% of adalimumab-treated patients and 2.4% of control-treated patients.

Across all adult indications in clinical trials, patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment. However, there have been very rare post-marketing reports of severe hepatic reactions including liver failure as well as less severe liver disorders that may precede liver failure, such as hepatitis including autoimmune hepatitis, in patients receiving TNF-blockers, including adalimumab. The causal relationship to adalimumab treatment remains unclear.

Concurrent treatment with azathioprine/6-mercaptopurine (6-MP)

In adult Crohn's disease studies, higher incidences of malignant and serious infection-related adverse events were seen with the combination of adalimumab and azathioprine/6-MP compared with adalimumab alone.

9.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Rheumatoid Arthritis

Description of Data Sources

The data described below reflect exposure to adalimumab in 3,046 patients, including more than 2,000 patients exposed for six months, and more than 1,500 exposed for more than one year (Studies DE009, DE011, DE019, DE031 and DE013). Adalimumab was studied in placebo-controlled trials and in long-term follow-up studies for up to 60 months duration in patients with moderately to severely active rheumatoid arthritis who had failed previous DMARD therapy; the mean age was 54 years, 77% were female and 91% Caucasian (Studies DE009, DE011, DE019, DE031). A further study (Study DE013) was in patients with recently diagnosed rheumatoid arthritis who had not previously been treated with MTX. Most patients received adalimumab 40 mg every other week.

Relative Frequency of Adverse Drug Reactions

Table 4 summarizes adverse drug reactions reported at a rate of at least 1% in patients treated with adalimumab 40 mg every other week, as well as all doses of adalimumab tested, compared to placebo or MTX (Study DE013). Adverse reaction rates in patients treated with adalimumab 40 mg weekly were similar to rates in patients treated with adalimumab every other week. In Study DE019, the types and frequencies of adverse drug reactions in the 10-year open-label extension were similar to those observed in the one-year double-blind portion.

Table 4 Number and Percentage of Patients with \geq 1% Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During the Control Period in Rheumatoid Arthritis Studies (Studies DE009, DE011, DE019, DE031, DE013)

| System Organ Class (SOC) | Adalimumab 40 mg SC eow N = 1247 n (%) | Adalimumab (all adalimumab) N = 1922 n (%) | Placebo (not Study DE013) N = 690 n (%) | MTX (Study DE013) N = 257 n (%) |
|---|---|---|--|--|
| Gastrointestinal Disorders | | | | |
| Nausea | 80 (6.4) | 112 (5.8) | 12 (1.7) | 33 (12.8) |
| Diarrhea | 47 (3.8) | 60 (3.1) | 17 (2.5) | 18 (7.0) |
| Abdominal pain | 22 (1.8) | 29 (1.5) | 5 (0.7) | 3 (1.2) |
| Abdominal pain upper | 20 (1.6) | 25 (1.3) | 0 (0.0) | 13 (5.1) |
| Mouth ulceration | 17 (1.4) | 24 (1.2) | 5 (0.7) | 12 (4.7) |
| Dyspepsia | 14 (1.1) | 21 (1.1) | 4 (0.6) | 7 (2.7) |
| Vomiting | 16 (1.3) | 20 (1.0) | 5 (0.7) | 6 (2.3) |
| General Disorders and Administration Site Conditions | | | | |
| Injection site irritation | 74 (5.9) | 122 (6.3) | 61 (8.8) | 3 (1.2) |
| Injection site reaction | 49 (3.9) | 67 (3.5) | 3 (0.4) | 2 (0.8) |
| Injection site pain | 36 (2.9) | 63 (3.3) | 24 (3.5) | 6 (2.3) |
| Injection site erythema | 36 (2.9) | 60 (3.1) | 2 (0.3) | 1 (0.4) |
| Fatigue | 37 (3.0) | 58 (3.0) | 7 (1.0) | 9 (3.5) |
| Injection site rash | 17 (1.4) | 22 (1.1) | 2 (0.3) | 0 (0.0) |
| Influenza-like illness | 15 (1.2) | 21 (1.1) | 2 (0.3) | 8 (3.1) |
| Pyrexia | 13 (1.0) | 20 (1.0) | 1 (0.1) | 6 (2.3) |

| System Organ Class (SOC) | Adalimumab 40 mg SC eow N = 1247 n (%) | Adalimumab (all adalimumab) N = 1922 n (%) | Placebo (not Study DE013) N = 690 n (%) | MTX (Study DE013) N = 257 n (%) |
|--|---|---|--|--|
| Infections and Infestations | | | | |
| Nasopharyngitis | 61 (4.9) | 95 (4.9) | 10 (1.5) | 28 (10.9) |
| Upper respiratory infection | 72 (5.8) | 93 (4.8) | 15 (2.2) | 17 (6.6) |
| Sinusitis | 46 (3.7) | 55 (2.9) | 17 (2.5) | 4 (1.6) |
| Herpes simplex | 33 (2.6) | 48 (2.5) | 6 (0.9) | 5 (1.9) |
| Urinary tract infection | 31 (2.5) | 44 (2.3) | 6 (0.9) | 7 (2.7) |
| Bronchitis | 19 (1.5) | 29 (1.5) | 8 (1.2) | 9 (3.5) |
| Herpes zoster | 17 (1.4) | 23 (1.2) | 8 (1.2) | 2 (0.8) |
| Influenza | 16 (1.3) | 21 (1.1) | 7 (1.0) | 5 (1.9) |
| Pneumonia | 17 (1.4) | 21 (1.1) | 3 (0.4) | 1 (0.4) |
| Investigations | | | | |
| Lymphocyte count decreased | 11 (0.9) | 38 (2.0) | 11 (1.6) | 1 (0.4) |
| Alanine aminotransferase increased | 27 (2.2) | 33 (1.7) | 4 (0.6) | 9 (3.5) |
| Liver function test abnormal | 19 (1.5) | 22 (1.1) | 4 (0.6) | 7 (2.7) |
| Musculoskeletal and Connective Tissue Disorders | | | | |
| Rheumatoid arthritis | 11 (0.9) | 28 (1.5) | 7 (1.0) | 2 (0.8) |
| Nervous System Disorders | | | | |
| Headache | 75 (6.0) | 124 (6.5) | 14 (2.0) | 14 (5.4) |
| Dizziness | 23 (1.8) | 32 (1.7) | 6 (0.9) | 3 (1.2) |
| Respiratory, Thoracic and Mediastinal Disorders | | | | |
| Pharyngolaryngeal pain | 33 (2.6) | 44 (2.3) | 9 (1.3) | 7 (2.7) |
| Cough | 31 (2.5) | 42 (2.2) | 4 (0.6) | 9 (3.5) |
| Skin and Subcutaneous Tissue Disorders | | | | |
| Rash | 44 (3.5) | 66 (3.4) | 9 (1.3) | 8 (3.1) |
| Pruritus | 28 (2.2) | 43 (2.2) | 4 (0.6) | 5 (1.9) |
| Alopecia | 22 (1.8) | 28 (1.5) | 2 (0.3) | 6 (2.3) |
| Rash pruritic | 14 (1.1) | 22 (1.1) | 0 (0.0) | 3 (1.2) |
| Definition(s): SC = subcutaneous; eow = every other week | | | | |

Psoriatic Arthritis

Table 5 summarizes adverse drug reactions reported in placebo-controlled and open-label studies at a rate of at least 1% in psoriatic arthritis patients treated with adalimumab 40 mg every other week.

Table 5 Number and Percentage of Patients with \geq 1% Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During the Control and Open-Label Periods in Psoriatic Arthritis Studies (Studies M02-518, M02-570, and M02-537)

| System Organ Class (SOC) | Double-Blind Study | | Open-Label Study |
|---|-----------------------------|--|--|
| | Placebo N = 211 n (%) | Adalimumab 40 mg SC eow N = 202 n (%) | Adalimumab 40 mg SC eow N = 382 n (%) |
| Gastrointestinal Disorders | | | |
| Nausea | 2 (0.9) | 2 (1.0) | 3 (0.8) |
| General Disorders and Administration Site Conditions | | | |
| Injection site reaction | 5 (2.4) | 11 (5.4) | 21 (5.5) |
| Injection site pain | 8 (3.8) | 8 (4.0) | 2 (0.5) |
| Injection site erythema | 0 (0.0) | 4 (2.0) | 2 (0.5) |
| Injection site burning | 4 (1.9) | 4 (2.0) | 4 (1.0) |
| Fatigue | 5 (2.4) | 0 (0.0) | 4 (1.0) |
| Infections and Infestations | | | |
| Upper respiratory infection | 7 (3.3) | 8 (4.0) | 17 (4.5) |
| Herpes simplex | 3 (1.4) | 6 (3.0) | 7 (1.8) |
| Skin fungal infection NOS | 0 (0.0) | 3 (1.5) | - |
| Pharyngitis | 1 (0.5) | 2 (1.0) | 4 (1.0) |
| Sinusitis | 4 (1.9) | 2 (1.0) | 12 (3.1) |
| Urinary tract infection | 0 (0.0) | 2 (1.0) | 6 (1.6) |
| Bronchitis | 1 (0.5) | 1 (0.5) | 5 (1.3) |
| Nasopharyngitis | 2 (0.9) | 1 (0.5) | 8 (2.1) |
| Influenza | 2 (0.9) | 0 (0.0) | 5 (1.3) |
| Investigations | | | |
| Liver function tests abnormal | 1 (0.5) | 2 (1.0) | 5 (1.3) |
| Nervous System Disorders | | | |
| Headache | 5 (2.4) | 5 (2.5) | 5 (1.3) |
| Paresthesia | 1 (0.5) | 3 (1.5) | 2 (0.5) |
| Respiratory, Thoracic, and Mediastinal Disorders | | | |
| Rhinitis NOS | 0 (0.0) | 3 (1.5) | 3 (0.8) |
| Skin and Subcutaneous Tissue Disorders | | | |
| Erythema | 0 (0.0) | 3 (1.5) | - |

Definition(s): SC = subcutaneous; eow = every other week

Ankylosing Spondylitis

Adalimumab has been studied in 393 patients with ankylosing spondylitis in two placebo-controlled studies. The safety profile for patients with ankylosing spondylitis treated with adalimumab 40 mg every other week was similar to the safety profile seen in patients with rheumatoid arthritis, adalimumab Studies DE009, DE011, DE019, and DE031. [Table 6](#) summarizes adverse drug reactions reported at a rate of at least 1% in ankylosing spondylitis patients treated with adalimumab 40 mg every other week compared to placebo.

Table 6 Number and Percentage of Patients with \geq 1% Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During the Control Period in Ankylosing Spondylitis Studies (Studies M03-607 and M03-606)

| System Organ Class (SOC) | Adalimumab 40 mg SC eow N = 246 n (%) | Placebo N = 151 n (%) |
|---|--|--------------------------------------|
| General Disorders and Administration Site Conditions | | |
| Fatigue | 5 (2.0) | 3 (2.0) |
| Injection site erythema | 5 (2.0) | 1 (0.7) |
| Injection site irritation | 4 (1.6) | 2 (1.3) |
| Injection site pain | 6 (2.4) | 3 (2.0) |
| Injection site reaction | 8 (3.3) | 1 (0.7) |
| Infections and Infestations | | |
| Nasopharyngitis | 8 (3.3) | 0 (0.0) |
| Upper respiratory tract infection | 5 (2.0) | 2 (1.3) |
| Nervous System Disorders | | |
| Dizziness | 3 (1.2) | 3 (2.0) |
| Headache | 11 (4.5) | 4 (2.6) |
| Skin and Subcutaneous Tissue Disorders | | |
| Eczema | 3 (1.2) | 1 (0.7) |
| Pruritis | 4 (1.6) | 1 (0.7) |
| Pruritis generalized | 3 (1.2) | 0 (0.0) |
| Rash | 4 (1.6) | 1 (0.7) |
| Urticaria | 3 (1.2) | 0 (0.0) |

Definition(s): SC = subcutaneous; eow = every other week

Crohn's Disease

Adalimumab has been studied in over 1,500 patients with Crohn's disease in five placebo-controlled and two open-label extension studies. The safety profile for patients with Crohn's disease treated with adalimumab was similar to the safety profile seen in patients with rheumatoid arthritis including the safety profile for patients in placebo-controlled Study M05-769. No new safety signals occurred during the open-label long-term studies with adalimumab exposure up to five years. The safety profile of adalimumab in Crohn's disease remains unaltered.

Table 7 and Table 8 summarize adverse drug reactions reported at a rate of at least 1% in Crohn's disease patients treated with adalimumab in induction and maintenance studies, respectively.

Table 7 Number and Percentage of Patients with \geq 1% Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During Administration of Induction Study Medications in Crohn's Disease Studies (Studies M02-403 and M04-691)

| System Organ Class (SOC) | Adalimumab 160/80 mg N = 235 n (%) | Adalimumab 80/40 mg N = 75 n (%) | Placebo N = 240 n (%) |
|---|---|---|-----------------------------|
| Eye Disorders | | | |
| Corneal pigmentation | 0 (0.0) | 1 (1.3) | 0 (0.0) |
| Visual disturbance | 0 (0.0) | 1 (1.3) | 0 (0.0) |
| Gastrointestinal Disorders | | | |
| Abdominal pain | 5 (2.1) | 0 (0.0) | 2 (0.8) |
| Abdominal pain lower | 3 (1.3) | 0 (0.0) | 0 (0.0) |
| Change of bowel habit | 0 (0.0) | 1 (1.3) | 0 (0.0) |
| Cheilitis | 0 (0.0) | 1 (1.3) | 1 (0.4) |
| Constipation | 2 (0.9) | 1 (1.3) | 3 (1.3) |
| Crohn's disease | 2 (0.9) | 1 (1.3) | 3 (1.3) |
| Flatulence | 3 (1.3) | 0 (0.0) | 0 (0.0) |
| Nausea | 6 (2.6) | 0 (0.0) | 4 (1.7) |
| Vomiting | 1 (0.4) | 1 (1.3) | 3 (1.3) |
| General Disorders and Administration Site Conditions | | | |
| Asthenia | 0 (0.0) | 1 (1.3) | 1 (0.4) |
| Chills | 0 (0.0) | 2 (2.7) | 1 (0.4) |
| Fatigue | 2 (0.9) | 1 (1.3) | 10 (4.2) |
| Influenza like illness | 0 (0.0) | 2 (2.7) | 2 (0.8) |
| Injection site bruising | 5 (2.1) | 1 (1.3) | 1 (0.4) |
| Injection site erythema | 4 (1.7) | 0 (0.0) | 0 (0.0) |
| Injection site irritation | 19 (8.1) | 8 (10.7) | 14 (5.8) |
| Injection site pain | 6 (2.6) | 4 (5.3) | 9 (3.8) |
| Injection site pruritus | 3 (1.3) | 0 (0.0) | 0 (0.0) |
| Injection site reaction | 11 (4.7) | 5 (6.7) | 6 (2.5) |

| System Organ Class (SOC) | Adalimumab 160/80 mg N = 235 n (%) | Adalimumab 80/40 mg N = 75 n (%) | Placebo N = 240 n (%) |
|--|---|---|--------------------------------------|
| Pain | 2 (0.9) | 1 (1.3) | 3 (1.3) |
| Pyrexia | 3 (1.3) | 3 (1.3) | 3 (1.3) |
| Infections and Infestations | | | |
| Staphylococcal infection | 0 (0.0) | 1 (1.3) | 0 (0.0) |
| Investigations | | | |
| Double stranded DNA antibody | 0 (0.0) | 1 (1.3) | 0 (0.0) |
| White blood cell count increased | 0 (0.0) | 1 (1.3) | 0 (0.0) |
| Metabolism and Nutrition Disorders | | | |
| Hypokalemia | 0 (0.0) | 1 (1.3) | 0 (0.0) |
| Musculoskeletal and Connective Tissue Disorders | | | |
| Arthralgia | 3 (1.3) | 1 (1.3) | 2 (0.8) |
| Back pain | 0 (0.0) | 1 (1.3) | 0 (0.0) |
| Muscle spasms | 0 (0.0) | 1 (1.3) | 1 (0.4) |
| Pain in extremity | 0 (0.0) | 1 (1.3) | 0 (0.0) |
| Nervous System Disorders | | | |
| Dizziness | 3 (1.3) | 0 (0.0) | 2 (0.8) |
| Headache | 8 (3.4) | 2 (2.7) | 7 (2.9) |
| Restless legs syndrome | 0 (0.0) | 1 (1.3) | 0 (0.0) |
| Reproductive System and Breast Disorders | | | |
| Genital pruritus female | 0 (0.0) | 1 (1.3) | 0 (0.0) |
| Skin and Subcutaneous Tissue Disorders | | | |
| Eczema | 1 (0.4) | 1 (1.3) | 0 (0.0) |
| Erythema | 1 (0.4) | 1 (1.3) | 1 (0.4) |
| Hyperhidrosis | 0 (0.0) | 1 (1.3) | 0 (0.0) |
| Onychorrhexis | 0 (0.0) | 1 (1.3) | 0 (0.0) |
| Pruritus | 1 (0.4) | 0 (0.0) | 4 (1.7) |
| Rash | 2 (0.9) | 2 (2.7) | 1 (0.4) |
| Rash maculo-papular | 1 (0.4) | 1 (1.3) | 0 (0.0) |
| Rash pruritic | 0 (0.0) | 1 (1.3) | 1 (0.4) |

Table 8 Number and Percentage of Patients with \geq 1% Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During Administration of Blinded Study Maintenance Medications in Crohn's Disease Studies (Studies M02-404 and M02-433)

| System Organ Class (SOC) | Adalimumab 40 mg SC eow, 40 mg ew N = 554 n (%) | Placebo N = 279 n (%) |
|---|--|-----------------------------|
| Gastrointestinal Disorders | | |
| Abdominal pain | 7 (1.3) | 4 (1.4) |
| Crohn's disease | 9 (1.6) | 9 (3.2) |
| Diarrhea | 7 (1.3) | 1 (0.4) |
| Nausea | 9 (1.6) | 5 (1.8) |
| General Disorders and Administration Site Conditions | | |
| Fatigue | 10 (1.8) | 1 (0.4) |
| Injection site bruising | 6 (1.1) | 1 (0.4) |
| Injection site erythema | 10 (1.8) | 0 (0.0) |
| Injection site irritation | 18 (3.2) | 2 (0.7) |
| Injection site pain | 8 (1.4) | 2 (0.7) |
| Injection site reaction | 26 (4.7) | 1 (0.4) |
| Pyrexia | 7 (1.3) | 5 (1.8) |
| Infections and Infestations | | |
| Herpes simplex | 6 (1.1) | 4 (1.4) |
| Nasopharyngitis | 8 (1.4) | 2 (0.7) |
| Rhinitis | 7 (1.3) | 1 (0.4) |
| Musculoskeletal and Connective Tissue Disorders | | |
| Arthralgia | 9 (1.6) | 2 (0.7) |
| Nervous System Disorders | | |
| Headache | 19 (3.4) | 6 (2.2) |
| Skin and Subcutaneous Tissue Disorder | | |
| Rash | 11 (2.0) | 5 (1.8) |
| Definition(s): SC = subcutaneous; ew = every week; eow = every other week | | |

Ulcerative Colitis

Adalimumab has been studied in 1,010 patients with ulcerative colitis in two placebo-controlled studies and one open-label extension study. The safety profile for patients with ulcerative colitis treated with adalimumab was similar to the safety profile observed in patients with Crohn's Disease.

Table 9 and Table 10 summarize adverse drug reactions reported at a rate of at least 1% in ulcerative colitis disease patients treated with adalimumab during induction and maintenance periods, respectively.

Table 9 Number and Percentage of Subjects \geq 1% Reporting Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During Administration of Induction Study Medications in Ulcerative Colitis Studies (Studies M06-826 and M06-827)

| System Organ Class (SOC) | Adalimumab 160/80 mg N = 480 n (%) | Adalimumab 80/40 mg N = 130 n (%) | Placebo N = 483 n (%) |
|---|---|--|--------------------------------------|
| Gastrointestinal Disorders | 17 (3.5) | 7 (5.4) | 27 (5.6) |
| Abdominal pain | 0 (0.0) | 2 (1.5) | 2 (0.4) |
| Colitis Ulcerative | 7 (1.5) | 2 (1.5) | 8 (1.7) |
| Nausea | 6 (1.3) | 1 (0.8) | 7 (1.4) |
| General Disorders and Administration Site Conditions | 44 (9.2) | 8 (6.2) | 34 (7.0) |
| Fatigue | 9 (1.9) | 1 (0.8) | 7 (1.4) |
| Influenza like illness | 1 (0.2) | 1 (0.8) | 5 (1.0) |
| Injection site erythema | 8 (1.7) | 1 (0.8) | 2 (0.4) |
| Injection Site Hematoma | 2 (0.4) | 2 (1.5) | 0 (0.0) |
| Injection site pain | 11 (2.3) | 2 (1.5) | 11 (2.3) |
| Injection site pruritus | 6 (1.3) | 1 (0.8) | 1 (0.2) |
| Injection site reaction | 5 (1.0) | 1 (0.8) | 2 (0.4) |
| Pyrexia | 3 (0.6) | 1 (0.8) | 7 (1.4) |
| Infections and Infestations | 19 (4.0) | 7 (5.4) | 24 (5.0) |
| Herpes simplex | 0 (0.0) | 2 (1.5) | 0 (0.0) |
| Nasopharyngitis | 5 (1.0) | 1 (0.8) | 4 (0.8) |
| Oral herpes | 2 (0.4) | 2 (1.5) | 2 (0.4) |
| Nervous System Disorders | 14 (2.9) | 2 (1.5) | 25 (5.2) |
| Headache | 7 (1.5) | 2 (1.5) | 20 (4.1) |
| Psychiatric Disorders | 1 (0.2) | 2 (1.5) | 4 (0.8) |
| Anxiety | 0 (0.0) | 2 (1.5) | 0 (0.0) |
| Skin and Subcutaneous Tissue Disorders | 19 (4.0) | 8 (6.2) | 17 (3.5) |
| Erythema | 5 (1.0) | 2 (1.5) | 1 (0.2) |
| Rash | 2 (0.4) | 2 (3.1) | 1 (0.2) |

Table 10 Number and Percentage of Subjects \geq 1% Reporting Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug During the Double-blind Induction and Maintenance Periods of Ulcerative Colitis Studies (Studies M06-826 and M06-827)

| System Organ Class (SOC) | Adalimumab 160/80 mg N = 480 n (%) | Placebo N = 483 n (%) |
|---|---|--------------------------------------|
| Gastrointestinal Disorders | 31 (6.5) | 36 (7.5) |
| Colitis ulcerative | 12 (2.5) | 14 (2.9) |
| Nausea | 9 (1.9) | 9 (1.9) |
| General Disorders and Administration Site Conditions | 64 (13.3) | 38 (7.9) |
| Fatigue | 10 (2.1) | 8 (1.7) |
| Influenza like illness | 3 (0.6) | 5 (1.0) |
| Injection site erythema | 15 (3.1) | 3 (0.6) |
| Injection site pain | 11 (2.3) | 12 (2.5) |
| Injection site pruritus | 9 (1.9) | 2 (0.4) |
| Injection site reaction | 11 (2.3) | 2 (0.4) |
| Injection site swelling | 5 (1.0) | 0 (0.0) |
| Malaise | 5 (1.0) | 2 (0.4) |
| Edema peripheral | 5 (1.0) | 1 (0.2) |
| Pyrexia | 3 (0.6) | 9 (1.9) |
| Infections and Infestations | 40 (8.3) | 42 (8.7) |
| Influenza | 0 (0.0) | 5 (1.0) |
| Nasopharyngitis | 9 (1.9) | 7 (1.4) |
| Upper respiratory tract infection | 5 (1.0) | 7 (1.4) |
| Musculoskeletal and Connective Tissue Disorders | 12 (2.5) | 12 (2.5) |
| Arthralgia | 5 (1.0) | 4 (0.8) |
| Nervous System Disorders | 19 (4.0) | 28 (5.8) |
| Headache | 10 (2.1) | 22 (4.6) |
| Skin and Subcutaneous Tissue Disorders | 38 (7.9) | 29 (6.0) |
| Erythema | 6 (1.3) | 2 (0.4) |
| Pruritus | 5 (1.0) | 5 (1.0) |
| Rash | 7 (1.5) | 5 (1.0) |

Serious adverse events resulting in hospitalizations were reported by 18% (67/379) in the adalimumab-treated patients compared to 26% (56/214) in the placebo group adjusted for patient years at risk.

During the double-blind controlled clinical trials, the most common ($\geq 5\%$) adverse drug reactions in subjects receiving adalimumab 160/80 during induction were ulcerative colitis (n = 35, 7.3%) and nasopharyngitis (n = 26, 5.4%), and during maintenance were ulcerative colitis (n = 38, 16.2%), nasopharyngitis (n = 26, 11.1%), abdominal pain (n = 17, 7.3%), and arthralgia (n = 17, 7.3%). There were 2/480 adalimumab-treated patients who experienced severe leukopenia of which one case was serious. The patient with serious leukopenia, which was considered secondary to 6-MP, had an associated viral infection.

During the double-blind controlled clinical trials, the most common serious adverse event occurring in > 1 patient more often in the adalimumab-treated patients compared to placebo when adjusted for exposure was deep vein thrombosis reported in 2 patients (4%, 1.12 events/100 patient-years).

During the double-blind controlled clinical trials, severe adverse events reported in >1 patient occurring more often in the adalimumab-treated patients compared to placebo when adjusted for exposure were deep vein thrombosis reported in 3 patients (0.6%, 1.68 events/100 patient-years), and constipation, leukopenia and fatigue, which were reported in 2 patients (0.4%, 1.12 events/100 patients-years).

The most common adverse event associated with discontinuation reported in > 1 subject during induction and maintenance was ulcerative colitis [n = 18 (3.8%) and n = 8 (3.4%), respectively].

Hidradenitis Suppurativa

Adalimumab has been studied in 727 adult patients with hidradenitis suppurativa in three placebo-controlled studies and one open-label extension study.

[Table 11](#) summarizes adverse drug reactions reported at a rate of at least 1% in hidradenitis suppurativa patients treated with adalimumab during the placebo-controlled portion of the studies.

Table 11 Number and Percentage of Patients ≥1% Reporting Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug in Controlled Hidradenitis Suppurativa Studies (Studies M10-467, M11-313 and M11-810)

| System Organ Class (SOC) | Adalimumab 40 mg eow N = 52 n (%) | Adalimumab 40 mg ew N = 367 n (%) | Placebo N = 366 n (%) |
|---|--|--|--------------------------------------|
| Eye Disorders | | | |
| Cataract | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| Conjunctivitis | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| Vision blurred | 1 (1.9) | 1 (0.3) | 0 (0.0) |
| Gastrointestinal Disorders | | | |
| Abdominal pain | 1 (1.9) | 1 (0.3) | 0 (0.0) |
| Abdominal pain upper | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| Diarrhoea | 1 (1.9) | 8 (2.2) | 3 (0.8) |
| Nausea | 1 (1.9) | 6 (1.6) | 8 (2.2) |
| Vomiting | 1 (1.9) | 3 (0.8) | 3 (0.8) |
| General Disorders and Administration Site Conditions | | | |
| Asthenia | 0 (0.0) | 1 (0.3) | 5 (1.4) |
| Chills | 1 (1.9) | 0 (0.0) | 1 (0.3) |
| Fatigue | 1 (1.9) | 4 (1.1) | 4 (1.1) |
| Injection site erythema | 0 (0.0) | 5 (1.4) | 0 (0.0) |
| Injection site pain | 0 (0.0) | 6 (1.6) | 6 (1.6) |
| Injection site pruritus | 0 (0.0) | 5 (1.4) | 0 (0.0) |
| Injection site reaction | 1 (1.9) | 3 (0.8) | 1 (0.3) |
| Edema | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| Pain | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| Pyrexia | 1 (1.9) | 1 (0.3) | 1 (0.3) |
| Infections and Infestations | | | |
| Bronchitis | 0 (0.0) | 2 (0.5) | 5 (1.4) |
| Cellulitis | 0 (0.0) | 0 (0.0) | 4 (1.1) |
| Gastroenteritis | 1 (1.9) | 2 (0.5) | 0 (0.0) |
| Herpes simplex | 2 (3.8) | 0 (0.0) | 1 (0.3) |
| Localised infection | 1 (1.9) | 1 (0.3) | 0 (0.0) |
| Nasopharyngitis | 3 (5.8) | 11 (3.0) | 9 (2.5) |
| Pneumonia | 1 (1.9) | 0 (0.0) | 3 (0.8) |
| Skin bacterial infection | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| Tooth abscess | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| Upper respiratory tract infection | 3 (5.8) | 7 (1.9) | 6 (1.6) |
| Urinary tract infection | 0 (0.0) | 3 (0.8) | 4 (1.1) |
| Vaginal infection | 1 (1.9) | 0 (0.0) | 0 (0.0) |

| System Organ Class (SOC) | Adalimumab 40 mg eow N = 52 n (%) | Adalimumab 40 mg ew N = 367 n (%) | Placebo N = 366 n (%) |
|--|--|--|-----------------------------|
| Musculoskeletal and Connective Tissue Disorders | | | |
| Arthralgia | 0 (0.0) | 5 (1.4) | 0 (0.0) |
| Pain in extremity | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| Nervous System Disorders | | | |
| Dizziness | 1 (1.9) | 6 (1.6) | 1 (0.3) |
| Dysgeusia | 1 (1.9) | 2 (0.5) | 0 (0.0) |
| Headache | 4 (7.7) | 17 (4.6) | 11 (3.0) |
| Respiratory, Thoracic and Mediastinal Disorders | | | |
| Cough | 0 (0.0) | 4 (1.1) | 2 (0.5) |
| Dyspnea | 1 (1.9) | 1 (0.3) | 1 (0.3) |
| Interstitial lung disease | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| Nasal congestion | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| Oropharyngeal pain | 1 (1.9) | 1 (0.3) | 0 (0.0) |
| Sneezing | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| Skin and Subcutaneous Tissue Disorders | | | |
| Hidradenitis | 2 (3.8) | 11 (3.0) | 16 (4.4) |
| Pruritus | 2 (3.8) | 2 (0.5) | 1 (0.3) |
| Pruritus generalized | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| Definition(s): ew = every week; eow = every other week | | | |

Psoriasis

Adalimumab has been studied in 1,696 patients with psoriasis in placebo-controlled and open-label extension studies. The safety profile for patients with psoriasis treated with adalimumab was similar to the safety profile seen in patients with rheumatoid arthritis. Safety results of the long-term open-label study are consistent with the known safety profile of adalimumab in other psoriasis studies. [Table 12](#) summarizes adverse drug reactions reported at a rate of at least 1% in psoriasis patients treated with an initial dose of adalimumab 80 mg followed by adalimumab 40 mg every other week compared to placebo or MTX.

Table 12 Number and Percentage of Patients \geq 1% Reporting Treatment-Emergent Adverse Events Possibly or Probably Related to Study Drug in Controlled Psoriasis Studies (Studies M03-656, M04-716 and M02-528)

| System Organ Class (SOC) | Adalimumab 80 mg x 1, then 40 mg SC eow N = 966 n (%) | Placebo + MTX N = 613 n (%) |
|--|---|-----------------------------------|
| Gastrointestinal | | |
| Nausea | 10 (1.0) | 11 (1.8) |
| General Disorders and Administration Conditions | | |
| Injection site reaction | 29 (3.0) | 9 (1.5) |
| Injection site irritation | 16 (1.7) | 6 (1.0) |
| Injection site pain | 14 (1.5) | 9 (1.5) |
| Fatigue | 10 (1.0) | 5 (0.8) |
| Infections and Infestations | | |
| Upper respiratory infections | 12 (1.2) | 3 (0.5) |
| Musculoskeletal and Connective Tissue Disorders | | |
| Arthralgia | 10 (1.0) | 3 (0.5) |
| Nervous System Disorders | | |
| Headache | 19 (2.0) | 14 (2.3) |
| Definition(s): SC = subcutaneous; eow = every other week; MTX = methotrexate | | |

Uveitis

Adalimumab has been studied in 500 adult patients with uveitis in two placebo-controlled studies and one open-label extension study. The safety profile for adult patients with uveitis treated with adalimumab was consistent with the known safety profile of adalimumab. Safety results of the long-term open-label study are generally consistent with the known safety profile of adalimumab in the controlled uveitis studies; the exposure-adjusted incidence rates of severe and serious adverse events (including serious infections) were higher in patients who received concomitant systemic corticosteroids and immunosuppressants. [Table 13](#) summarizes adverse drug reactions reported at a rate of at least 1% in adult patients with uveitis treated with an initial dose of adalimumab 80 mg followed by adalimumab 40 mg every other week compared to placebo.

Table 13 Number and Percentage of Patients \geq 1% Reporting Treatment-Emergent Adverse Events Possibly or Probably Related to Study Drug in Controlled Adult Uveitis Studies (Studies M10-877 and M10-880)

| System Organ Class (SOC) | Adalimumab 80 mg x 1, then 40 mg SC eow N = 250; n (%) | Placebo N = 250; n (%) |
|---|---|-----------------------------------|
| Cardiac Disorders | 6 (2.4) | 1 (0.4) |
| Palpitations | 4 (1.6) | 1 (0.4) |
| Ear and Labyrinth Disorders | 2 (0.8) | 4 (1.6) |
| Tinnitus | 1 (0.4) | 3 (1.2) |
| Endocrine Disorders | 5 (2.0) | 4 (1.6) |
| Cushingoid | 3 (1.2) | 3 (1.2) |
| Eye Disorders | 20 (8.0) | 20 (8.0) |
| Cataract | 3 (1.2) | 4 (1.6) |
| Cataract subcapsular | 3 (1.2) | 1 (0.4) |
| Cystoid Macular Oedema | 3 (1.2) | 1 (0.4) |
| Uveitis | 3 (1.2) | 6 (2.4) |
| Gastrointestinal Disorders | 26 (10.4) | 17 (6.8) |
| Abdominal discomfort | 3 (1.2) | 1 (0.4) |
| Abdominal pain upper | 4 (1.6) | 2 (0.8) |
| Dry mouth | 4 (1.6) | 0 |
| Dyspepsia | 3 (1.2) | 2 (0.8) |
| Nausea | 5 (2.0) | 7 (2.8) |
| General Disorders and Administration Site Conditions | 50 (20.0) | 38 (15.2) |
| Fatigue | 13 (5.2) | 11 (4.4) |
| Injection site bruising | 2 (0.8) | 3 (1.2) |
| Injection site erythema | 4 (1.6) | 1 (0.4) |
| Injection site pain | 10 (4.0) | 12 (4.8) |
| Injection site rash | 6 (2.4) | 1 (0.4) |
| Injection site swelling | 4 (1.6) | 0 |
| Malaise | 2 (0.8) | 4 (1.6) |
| Oedema peripheral | 5 (2.0) | 3 (1.2) |
| Peripheral swelling | 3 (1.2) | 0 |
| Pyrexia | 4 (1.6) | 2 (0.8) |

| System Organ Class (SOC) | Adalimumab 80 mg x 1, then 40 mg SC eow N = 250; n (%) | Placebo N = 250; n (%) |
|--|---|-----------------------------------|
| Infections and Infestations | 51 (20.4) | 29 (11.6) |
| Bronchitis | 4 (1.6) | 3 (1.2) |
| Influenza | 1 (0.4) | 3 (1.2) |
| Nasopharyngitis | 14 (5.6) | 7 (2.8) |
| Rash pustular | 4 (1.6) | 0 |
| Upper respiratory tract infection | 7 (2.8) | 3 (1.2) |
| Urinary tract infection | 7 (2.8) | 5 (2.0) |
| Investigations | 32 (12.8) | 18 (7.2) |
| Alanine aminotransferase increased | 8 (3.2) | 1 (0.4) |
| Aspartate aminotransferase increased | 7 (2.8) | 0 |
| Blood creatinine increased | 3 (1.2) | 2 (0.8) |
| Blood pressure increased | 4 (1.6) | 0 |
| Intraocular pressure increased | 5 (2.0) | 3 (1.2) |
| Weight increased | 5 (2.0) | 2 (0.8) |
| White blood cell count increased | 3 (1.2) | 1 (0.4) |
| Metabolism and Nutrition Disorders | 12 (4.8) | 8 (3.2) |
| Diabetes mellitus | 0 | 4 (1.6) |
| Increased appetite | 1 (0.4) | 4 (1.6) |
| Musculoskeletal and Connective Tissue Disorders | 39 (15.6) | 30 (12.0) |
| Arthralgia | 14 (5.6) | 12 (4.8) |
| Back pain | 3 (1.2) | 1 (0.4) |
| Joint swelling | 2 (0.8) | 3 (1.2) |
| Muscle spasms | 5 (2.0) | 2 (0.8) |
| Musculoskeletal stiffness | 3 (1.2) | 2 (0.8) |
| Myalgia | 4 (1.6) | 3 (1.2) |
| Pain in extremity | 8 (3.2) | 1 (0.4) |
| Nervous System Disorders | 29 (11.6) | 16 (6.4) |
| Dizziness | 2 (0.8) | 4 (1.6) |
| Headache | 12 (4.8) | 12 (4.8) |
| Paraesthesia | 7 (2.8) | 1 (0.4) |
| Tremor | 4 (1.6) | 1 (0.4) |
| Psychiatric Disorders | 24 (9.6) | 10 (4.0) |
| Anxiety | 4 (1.6) | 0 |
| Insomnia | 13 (5.2) | 7 (2.8) |

| System Organ Class (SOC) | Adalimumab 80 mg x 1, then 40 mg SC eow N = 250; n (%) | Placebo N = 250; n (%) |
|--|---|-----------------------------------|
| Respiratory, Thoracic and Mediastinal Disorders | 18 (7.2) | 8 (3.2) |
| Cough | 5 (2.0) | 3 (1.2) |
| Dyspnoea | 2 (0.8) | 3 (1.2) |
| Skin and Subcutaneous Tissue Disorders | 40 (16.0) | 36 (14.4) |
| Acne | 5 (2.0) | 7 (2.8) |
| Alopecia | 3 (1.2) | 6 (2.4) |
| Dermatitis allergic | 3 (1.2) | 2 (0.8) |
| Eczema | 3 (1.2) | 1 (0.4) |
| Erythema | 4 (1.6) | 3 (1.2) |
| Hyperhidrosis | 6 (2.4) | 3 (1.2) |
| Pruritus | 5 (2.0) | 1 (0.4) |
| Rash | 3 (1.2) | 4 (1.6) |
| Vascular Disorders | 12 (4.8) | 10 (4.0) |
| Hot flush | 4 (1.6) | 2 (0.8) |
| Hypertension | 4 (1.6) | 3 (1.2) |

Definition(s): SC = subcutaneous; eow = every other week

During the double-masked controlled clinical trials, the most common ($\geq 5\%$) adverse drug reactions in adult subjects receiving adalimumab were nasopharyngitis (n = 44, 17.6%), arthralgia (n = 38, 15.2%), headache (n = 30, 12.0%), fatigue (n = 26, 10.4%), urinary tract infection (n = 21, 8.4%), uveitis (n = 20, 8.0%), back pain (n = 19, 7.6%), insomnia (n = 18, 7.2%), cough (n = 18, 7.2%), eye pain (n = 18, 7.2%), and upper respiratory tract infection (n = 15, 6.0%).

During the double-masked controlled clinical trials, the most common serious adverse event occurring in >1 patient more often in the adalimumab-treated patients compared to placebo was pneumonia (n = 2). During the overall adalimumab uveitis development program, including the double-masked controlled, and open-label extension trials, the most frequently reported serious adverse event was cataract (n = 7 patients).

During the double-masked controlled clinical trials, severe adverse events reported in > 1 patient occurring more often in the adalimumab-treated patients compared to placebo were diarrhea (n = 2) and pneumonia (n = 2). During the overall adalimumab uveitis development program, including the double-masked controlled, and open-label extension trials, the most common severe adverse events reported were hypertension (n = 5 patients), pneumonia, urinary tract infection, reduced visual acuity and severe vision loss (n = 4 patients each).

Other Common Clinical Trial Adverse Drug Reactions

Other clinical trial adverse reactions occurring at an incidence of $\geq 1\%$ that were observed among the various indications include:

Eye Disorders: conjunctivitis, visual impairment

Renal and Urinary Disorders: hematuria, renal impairment

9.3 Less Common Clinical Trial Adverse Reactions

Infrequent serious adverse drug reactions occurring at an incidence of less than 1% in patients treated with adalimumab in rheumatoid arthritis Studies DE009, DE011, DE019, DE031 and DE013, JIA Study DE038, psoriatic arthritis Studies M02-518 and M02-570, ankylosing spondylitis Studies M03-607 and M03-606, Crohn's disease Maintenance Studies M02-404 and M02-433, ulcerative colitis Studies M06-826 and M06-827, hidradenitis suppurativa studies M10-467, M11-313 and M11-810, Psoriasis Studies M03-656, M04-716, and M02-528, and adult uveitis Studies M10-877 and M10-880:

Blood and Lymphatic System Disorders: agranulocytosis, anemia, eosinophilia, leukopenia, lymphadenopathy, lymphocytosis, neutropenia, pancytopenia

Cardiac Disorders: arrhythmia supraventricular, cardiac arrest, chest pain, palpitations

Eye Disorders: blepharitis, diplopia, eye swelling

Gastrointestinal Disorders: abdominal pain, anal fistula, Crohn's disease, frequent bowel movements, hematochezia, hemorrhoidal hemorrhage, pancreatitis, rectal hemorrhage, small intestine obstruction

General Disorders and Administration Site Conditions: death, non-cardiac chest pain, pyrexia

Hepatobiliary Disorders: hepatic necrosis

Immune System Disorders: hypersensitivity

Infections and Infestations: abscess, abscess limb, arthritis bacterial, bronchitis, bronchopneumonia, cellulitis, cystitis, device-related infection, diverticulitis, erysipelas, escherichia sepsis, gastroenteritis, genital herpes, herpes virus infection, herpes zoster, histoplasmosis, infected skin ulcer, infection, lobar pneumonia, lower respiratory tract infection, meningitis viral, mycobacterium avium complex infection, necrotizing fasciitis, perianal abscess, pharyngitis, pneumonia, pneumonia pneumococcal, pyelonephritis, respiratory tract infection, sepsis, septic shock, sinusitis, tuberculosis, urinary tract infection, urosepsis, viral infection, wound infection

Injury, Poisoning and Procedural Complications: postoperative wound complication

Investigations: double-stranded DNA antibody, hepatic enzyme increased

Metabolism and Nutrition Disorders: hyperglycemia*

| | |
|---|--|
| Musculoskeletal and Connective Tissue Disorders: | arthritis, arthropathy, back pain, muscular weakness, musculoskeletal chest pain, osteitis, rheumatoid arthritis, systemic lupus erythematosus |
| Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps): | basal cell carcinoma, B-cell lymphoma, breast cancer, malignant melanoma <i>in situ</i> , metastases to liver, ovarian cancer, squamous cell carcinoma, testicular seminoma (pure) |
| Nervous System Disorders: | clonus, hyperreflexia, hydrocephalus, hypertensive encephalopathy, intention tremor, multiple sclerosis, paresthesia, tremor, neuropathy |
| Pregnancy, Puerperium and Perinatal Conditions: | abortion spontaneous |
| Psychiatric Disorders: | confusional state |
| Renal and Urinary Disorders: | nocturia |
| Reproductive System and Breast Disorders: | cervical dysplasia, endometrial hyperplasia |
| Respiratory, Thoracic and Mediastinal Disorders: | bronchospasm, lung infiltration, pleural effusion, pleurisy, pneumonitis, respiratory failure |
| Skin and Subcutaneous Tissue Disorders: | psoriasis, pustular psoriasis, rash |
| Surgical and Medical Procedures: | arthrodesis |
| Vascular Disorders: | Circulatory collapse, rheumatoid vasculitis |

*Hyperglycemia ADR in trials were non-serious

9.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

There are no known laboratory tests that may be helpful in following the patient's response or in identifying possible adverse reactions.

Pediatric

In the polyarticular JIA trial (Study DE038), 10/171 (5.8%) and 5/171 (2.9%) of patients treated with adalimumab developed severe elevations of ALT and AST (exceeding > 3 times the ULN of ALT and AST, respectively). Forty two (42)/171 (25%) developed elevations of creatine phosphokinase (CPK); with 10/171 (5.8%) patients with severe elevations.

Liver enzyme elevations were more frequent among those treated with the combination of adalimumab and MTX than treated with adalimumab alone (ALT: 9.5% vs. 2.3%; AST: 5.9% vs. 0%).

No ALT or AST elevations $\geq 3 \times$ ULN occurred in the open-label study of adalimumab in patients with polyarticular JIA who were 2 to < 4 years of age (Study M10-444).

In the Phase 3 trial of adalimumab in patients with pediatric Crohn's disease which evaluated efficacy and safety of two body weight adjusted maintenance dose regimens following body weight adjusted induction therapy up to 52 weeks of treatment, ALT elevations $\geq 3 \times$ ULN

occurred in 2.9% of patients all of whom were exposed to concomitant immunosuppressants at baseline.

The rates of hepatic adverse events were 7.7% (4/52) in the High-Dose group and 8.0% (4/50) in the Low-Dose group for pediatric patients 13 to 17 years of age weighing \geq 40 kg with Crohn's disease.

Adult

In controlled rheumatoid arthritis clinical trials (Studies DE009, DE011, DE019, and DE031), elevations of ALT were similar in patients receiving adalimumab or placebo. In patients with early rheumatoid arthritis (disease duration of less than three years) (Study DE013), elevations of ALT were more common in the combination arm (adalimumab + MTX) compared to the MTX monotherapy arm or the adalimumab monotherapy arm.

In psoriatic arthritis clinical trials, elevations in ALT were more common in psoriatic arthritis patients compared with patients in rheumatoid arthritis clinical studies.

In controlled Crohn's disease clinical trials and ulcerative colitis, elevations of ALT were similar in patients receiving adalimumab or placebo.

In all indications, patients with raised ALT were asymptomatic and in most cases, elevations were transient and resolved on continued treatment.

9.5 Clinical Trial Adverse Reactions (Pediatrics)

Polyarticular Juvenile Idiopathic Arthritis

Table 14 Number and Percentage of Subjects with \geq 1% Treatment-Emergent Events at Least Possibly Related to Study Drug During the Double Blind Placebo-Controlled Phase in the Polyarticular Juvenile Idiopathic Arthritis Trial (Study DE038)

| System Organ Class MedDRA 12.1 Preferred Term | MTX | | Non-MTX | | Overall | |
|---|----------------------------|-------------------------------|----------------------------|-------------------------------|----------------------------|-------------------------------|
| | Placebo N = 37 n (%) | Adalimumab N = 38 n (%) | Placebo N = 28 n (%) | Adalimumab N = 30 n (%) | Placebo N = 65 n (%) | Adalimumab N = 68 n (%) |
| Any at least possibly related adverse event | 17 (45.9) | 22 (57.9) | 9 (32.1) | 16 (53.3) | 26 (40.0) | 38 (55.9) |
| Blood and Lymphatic System Disorders | 0 | 2 (5.3) | 0 | 1 (3.3) | 0 | 3 (4.4) |
| Leukopenia | 0 | 1 (2.6) | 0 | 0 | 0 | 1 (1.5) |
| Neutropenia | 0 | 1 (2.6) | 0 | 1 (3.3) | 0 | 2 (2.9) |
| Ear and Labyrinth Disorders | 0 | 0 | 0 | 1 (3.3) | 0 | 1 (1.5) |
| Ear pain | 0 | 0 | 0 | 1 (3.3) | 0 | 1 (1.5) |
| Gastrointestinal Disorders | 1 (2.7) | 1 (2.6) | 0 | 0 | 1 (1.5) | 1 (1.5) |
| Gastroduodenitis | 1 (2.7) | 0 | 0 | 0 | 1 (1.5) | 0 |
| Vomiting | 0 | 1 (2.6) | 0 | 0 | 0 | 1 (1.5) |
| General Disorders and Administration Site Conditions | 10 (27.0) | 15 (39.5) | 6 (21.4) | 11 (36.7) | 16 (24.6) | 26 (38.2) |
| Application site reaction | 1 (2.7) | 1 (2.6) | 0 | 0 | 1 (1.5) | 1 (1.5) |
| Fatigue | 0 | 0 | 0 | 1 (3.3) | 0 | 1 (1.5) |
| Influenza like illness | 1 (2.7) | 0 | 0 | 0 | 1 (1.5) | 0 |
| Injection site erythema | 1 (2.7) | 2 (5.3) | 0 | 1 (3.3) | 1 (1.5) | 3 (4.4) |
| Injection site hematoma | 0 | 1 (2.6) | 0 | 0 | 0 | 1 (1.5) |
| Injection site hypersensitivity | 1 (2.7) | 0 | 0 | 0 | 1 (1.5) | 0 |
| Injection site pain | 7 (18.9) | 7 (18.4) | 3 (10.7) | 9 (30.0) | 10 (15.4) | 16 (23.5) |
| Injection site pruritus | 0 | 1 (2.6) | 0 | 1 (3.3) | 0 | 2 (2.9) |
| Injection site reaction | 1 (2.7) | 7 (18.4) | 1 (3.6) | 3 (10.0) | 2 (3.1) | 10 (14.7) |
| Pain | 0 | 1 (2.6) | 2 (7.1) | 2 (6.7) | 2 (3.1) | 3 (4.4) |

| System Organ Class MedDRA 12.1 Preferred Term | MTX | | Non-MTX | | Overall | |
|--|----------------------------|-------------------------------|----------------------------|-------------------------------|----------------------------|-------------------------------|
| | Placebo N = 37 n (%) | Adalimumab N = 38 n (%) | Placebo N = 28 n (%) | Adalimumab N = 30 n (%) | Placebo N = 65 n (%) | Adalimumab N = 68 n (%) |
| Pyrexia | 0 | 2 (5.3) | 0 | 0 | 0 | 2 (2.9) |
| Immune System Disorder | 0 | 1 (2.6) | 0 | 1 (3.3) | 0 | 2 (2.9) |
| Hypersensitivity | 0 | 1 (2.6) | 0 | 1 (3.3) | 0 | 2 (2.9) |
| Infections and Infestations | 7 (18.9) | 10 (26.3) | 3 (10.7) | 6 (20.0) | 10 (15.4) | 16 (23.5) |
| Acute tonsillitis | 1 (2.7) | 1 (2.6) | 0 | 0 | 1 (1.5) | 1 (1.5) |
| Bronchitis | 1 (2.7) | 0 | 0 | 1 (3.3) | 1 (1.5) | 1 (1.5) |
| Ear infection | 0 | 1 (2.6) | 0 | 1 (3.3) | 0 | 2 (2.9) |
| Folliculitis | 1 (2.7) | 0 | 0 | 0 | 1 (1.5) | 0 |
| Fungal infection | 0 | 0 | 1 (3.6) | 0 | 1 (1.5) | 0 |
| Herpes simplex | 0 | 0 | 0 | 1 (3.3) | 0 | 1 (1.5) |
| Herpes virus infection | 0 | 0 | 0 | 1 (3.3) | 0 | 1 (1.5) |
| Impetigo | 0 | 1 (2.6) | 0 | 1 (3.3) | 0 | 2 (2.9) |
| Influenza | 0 | 1 (2.6) | 1 (3.6) | 1 (3.3) | 1 (1.5) | 2 (2.9) |
| Molluscum contagiosum | 1 (2.7) | 0 | 0 | 0 | 1 (1.5) | 0 |
| Oral herpes | 1 (2.7) | 1 (2.6) | 0 | 0 | 1 (1.5) | 1 (1.5) |
| Paronychia | 0 | 1 (2.6) | 0 | 0 | 0 | 1 (1.5) |
| Pharyngotonsillitis | 1 (2.7) | 0 | 0 | 1 (3.3) | 1 (1.5) | 1 (1.5) |
| Rhinitis | 0 | 2 (5.3) | 0 | 1 (3.3) | 0 | 3 (4.4) |
| Sinusitis | 0 | 1 (2.6) | 0 | 0 | 0 | 1 (1.5) |
| Staphylococcal skin infection | 0 | 0 | 1 (3.6) | 0 | 1 (1.5) | 0 |
| Upper respiratory tract infection | 2 (5.4) | 3 (7.9) | 0 | 2 (6.7) | 2 (3.1) | 5 (7.4) |
| Urinary tract infection | 0 | 1 (2.6) | 0 | 0 | 0 | 1 (1.5) |
| Viral infection | 1 (2.7) | 3 (7.9) | 0 | 0 | 1 (1.5) | 3 (4.4) |

| System Organ Class MedDRA 12.1 Preferred Term | MTX | | Non-MTX | | Overall | |
|--|----------------------------|-------------------------------|----------------------------|-------------------------------|----------------------------|-------------------------------|
| | Placebo N = 37 n (%) | Adalimumab N = 38 n (%) | Placebo N = 28 n (%) | Adalimumab N = 30 n (%) | Placebo N = 65 n (%) | Adalimumab N = 68 n (%) |
| Viral upper respiratory tract infection | 0 | 0 | 0 | 1 (3.3) | 0 | 1 (1.5) |
| Injury, Poisoning and Procedural Complications | 1 (2.7)* | 0* | 1 (3.6) * | 0* | 2 (3.1) * | 0* |
| Excoriation† | 1 (2.7) | 4 (10.5) | 1 (3.6) | 3 (10.0) | 2 (3.1) | 7 (10.3) |
| Injury | 0 | 0 | 1 (3.6) | 0 | 1 (1.5) | 0 |
| Scratch | 1 (2.7) | 0 | 0 | 0 | 1 (1.5) | 0 |
| Investigations | 0 | 1 (2.6) | 0 | 0 | 0 | 1 (1.5) |
| Lymphocyte count increased | 0 | 1 (2.6) | 0 | 0 | 0 | 1 (1.5) |
| Neutrophil count decreased | 0 | 1 (2.6) | 0 | 0 | 0 | 1 (1.5) |
| Metabolism and Nutrition Disorders | 1 (2.7) | 0 | 0 | 0 | 1 (1.5) | 0 |
| Enzyme abnormality | 1 (2.7) | 0 | 0 | 0 | 1 (1.5) | 0 |
| Musculoskeletal and Connective Tissue Disorders | 3 (8.1) | 1 (2.6) | 0 | 1 (3.3) | 3 (4.6) | 2 (2.9) |
| Arthralgia | 0 | 0 | 0 | 1 (3.3) | 0 | 1 (1.5) |
| Groin pain | 1 (2.7) | 0 | 0 | 0 | 1 (1.5) | 0 |
| Juvenile arthritis | 1 (2.7) | 1 (2.6) | 0 | 0 | 1 (1.5) | 1 (1.5) |
| Rheumatoid arthritis | 1 (2.7) | 0 | 0 | 0 | 1 (1.5) | 0 |
| Nervous System Disorders | 1 (2.7) | 0 | 0 | 1 (3.3) | 1 (1.5) | 1 (1.5) |
| Headache | 1 (2.7) | 0 | 0 | 1 (3.3) | 1 (1.5) | 1 (1.5) |
| Renal and Urinary Disorders | 0 | 0 | 2 (7.1) | 0 | 2 (3.1) | 0 |
| Dysuria | 0 | 0 | 1 (3.6) | 0 | 1 (1.5) | 0 |
| Proteinuria | 0 | 0 | 1 (3.6) | 0 | 1 (1.5) | 0 |

| System Organ Class MedDRA 12.1 Preferred Term | MTX | | Non-MTX | | Overall | |
|--|----------------------------|-------------------------------|----------------------------|-------------------------------|----------------------------|-------------------------------|
| | Placebo N = 37 n (%) | Adalimumab N = 38 n (%) | Placebo N = 28 n (%) | Adalimumab N = 30 n (%) | Placebo N = 65 n (%) | Adalimumab N = 68 n (%) |
| Respiratory, Thoracic and Mediastinal Disorders | 0 | 2 (5.3) | 0 | 1 (3.3) | 0 | 3 (4.4) |
| Asthma | 0 | 1 (2.6) | 0 | 0 | 0 | 1 (1.5) |
| Cough | 0 | 0 | 0 | 1 (3.3) | 0 | 1 (1.5) |
| Epistaxis | 0 | 1 (2.6) | 0 | 0 | 0 | 1 (1.5) |
| Skin and Subcutaneous Tissue Disorders | 1 (2.7)* | 1 (2.6)* | 0 | 1 (3.3)* | 1 (1.5)* | 2 (2.9)* |
| Acne | 0 | 0 | 0 | 1 (3.3) | 0 | 1 (1.5) |
| Dermatitis | 1 (2.7) | 0 | 0 | 0 | 1 (1.5) | 0 |
| Rash† | 0 | 1 (2.6) | 0 | 2 (6.7) | 0 | 3 (4.4) |
| Rash papular | 0 | 0 | 0 | 1 (3.3) | 0 | 1 (1.5) |
| Skin lesion | 0 | 1 (2.6) | 0 | 0 | 0 | 1 (1.5) |

* Total only includes values for the terms that were considered possibly or probably related by the investigator.

† Term was not considered possibly or probably related as assessed by the investigator; however, these terms were considered more common in patients treated with adalimumab vs. placebo in the clinical trial.

Definition(s): MTX = methotrexate

In Study DE038, adalimumab was studied in 171 patients aged 4 to 17 years with polyarticular JIA. Serious adverse events were observed in 28% of patients treated with adalimumab and included neutropenia, streptococcal pharyngitis, increased aminotranferases, herpes zoster, myositis, metrorrhagia and appendicitis. Serious infections were observed in 6.4% of patients treated with adalimumab and included cases of herpes zoster, appendicitis, pneumonia, urinary tract infection, streptococcal pharyngitis, viral infection and cervicitis. A total of 45% of patients experienced an infection while receiving adalimumab with or without concomitant MTX in the first 16 weeks of treatment (see **WARNINGS AND PRECAUTIONS [8], Infections**). Granuloma annulare was reported in two patients (see **WARNINGS AND PRECAUTIONS [8], Malignancies**).

During the double-blind phase of Study DE038, the most common ($\geq 5\%$) adverse reactions occurring in the JIA population treated with adalimumab were viral infection (18%), injection site pain (18%), upper respiratory tract infection (16%), injection site reaction (15%), contusion (13%), excoriation (10%), rhinitis (7%), vomiting (6%) and drug hypersensitivity (6%).

Throughout Study DE038, 6% of patients had mild to moderate allergic reaction adverse events primarily localized allergic hypersensitivity reactions and urticaria (see **WARNINGS AND PRECAUTIONS [8], Hypersensitivity Reactions**).

In the JIA trial, 10% of patients treated with adalimumab who were negative at baseline for anti-double-stranded DNA antibodies developed positive titers after 48 weeks of treatment (see **ADVERSE REACTIONS, Adverse Reaction Overview [9.1], Immunogenicity, Pediatric**).

In Study M10-444, adalimumab was studied in 32 patients who were 2 to < 4 years of age or 4 years of age and older weighing < 15 kg with polyarticular JIA. The safety profile for this patient population was similar to the safety profile seen in Study DE038.

In Study M10-444, 78% of patients experienced an infection while receiving adalimumab. These included nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, and were mostly mild to moderate in severity. Serious infections were observed in 9% of patients receiving adalimumab in the study and included dental caries, rotavirus gastroenteritis, and varicella.

In Study M10-444, non-serious allergic reactions were observed in 6% of patients and included intermittent urticaria and rash, which were all mild in severity.

Pediatric Crohn's Disease

Table 15 summarizes adverse drug reactions reported in Study M06-806 at a rate of at least 1% in the indicated pediatric patient population with Crohn's disease treated with adalimumab.

Table 15 Number and Percentage of Patients with ≥ 1% Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug With Double-Blind Every Other Week Dosing in the Pediatric Crohn's Disease Study (Study M06-806)

| System Organ Class (SOC) | High-Dose 40 mg eow N = 52 n (%) | Low-Dose 20 mg eow N = 50 n (%) |
|---|---|--|
| Blood and Lymphatic System Disorders | 3 (5.8) | 1 (2.0) |
| Leukopenia | 2 (3.8) | 0 |
| Lymphadenitis | 1 (1.9) | 0 |
| Neutropenia | 1 (1.9) | 0 |
| Thrombocytosis | 0 | 1 (2.0) |
| Eye Disorders | 1 (1.9) | 1 (2.0) |
| Conjunctivitis | 0 | 1 (2.0) |
| Vision blurred | 1 (1.9) | 0 |
| Gastrointestinal Disorders | 2 (3.8) | 3 (6.0) |
| Abdominal pain | 0 | 1 (2.0) |
| Crohn's disease | 0 | 1 (2.0) |
| Diarrhoea | 1 (1.9) | 0 |
| Nausea | 1 (1.9) | 0 |
| Pancreatitis acute | 0 | 1 (2.0) |
| General Disorders and Administration Site Conditions | 10 (19.2) | 7 (14.0) |
| Injection site erythema | 1 (1.9) | 1 (2.0) |
| Injection site pain | 2 (3.8) | 1 (2.0) |
| Injection site pruritus | 0 | 1 (2.0) |
| Injection site rash | 0 | 1 (2.0) |
| Injection site reaction | 4 (7.7) | 2 (4.0) |
| Injection site swelling | 0 | 1 (2.0) |
| Injection site warmth | 0 | 1 (2.0) |
| Nodule | 1 (1.9) | 0 |
| Pain | 1 (1.9) | 0 |
| Pyrexia | 2 (3.8) | 1 (2.0) |
| Suprapubic pain | 0 | 1 (2.0) |

| System Organ Class (SOC) | High-Dose 40 mg eow N = 52 n (%) | Low-Dose 20 mg eow N = 50 n (%) |
|---|---|--|
| Infections and Infestations | 6 (11.5) | 11 (22.0) |
| Acute tonsillitis | 0 | 1 (2.0) |
| Bartholin's abscess | 0 | 1 (2.0) |
| Cellulitis pharyngeal | 0 | 1 (2.0) |
| Folliculitis | 1 (1.9) | 0 |
| Fungal infection | 0 | 1 (2.0) |
| Histoplasmosis disseminated | 1 (1.9) | 0 |
| Nasopharyngitis | 1 (1.9) | 1 (2.0) |
| Oral candidiasis | 1 (1.9) | 0 |
| Otitis externa | 0 | 1 (2.0) |
| Otitis media | 0 | 1 (2.0) |
| Pertussis | 0 | 1 (2.0) |
| Pharyngitis | 1 (1.9) | 0 |
| Pharyngitis streptococcal | 0 | 3 (6.0) |
| Staphylococcal infection | 0 | 1 (2.0) |
| Upper respiratory tract infection | 0 | 2 (4.0) |
| Urinary tract infection | 1 (1.9) | 0 |
| Viral pharyngitis | 0 | 1 (2.0) |
| Viral upper respiratory tract infection | 2 (3.8) | 2 (4.0) |
| Vulvovaginal mycotic infection | 1 (1.9) | 1 (2.0) |
| Injury, Poisoning and Procedural Complications | 1 (1.9) | 0 |
| Contusion | 1 (1.9) | 0 |
| Investigations | 4 (7.7) | 3 (6.0) |
| Alanine aminotransferase increased | 1 (1.9) | 2 (4.0) |
| Antinuclear antibody positive | 1 (1.9) | 0 |
| Aspartate aminotransferase increased | 1 (1.9) | 0 |
| Hepatic enzyme increased | 1 (1.9) | 0 |
| White blood cell count decreased | 0 | 1 (2.0) |
| Metabolism and Nutrition Disorders | 0 | 1 (2.0) |
| Hypertriglyceridaemia | 0 | 1 (2.0) |

| System Organ Class (SOC) | High-Dose 40 mg eow N = 52 n (%) | Low-Dose 20 mg eow N = 50 n (%) |
|---|---|--|
| Musculoskeletal and Connective Tissue Disorders | 3 (5.8) | 1 (2.0) |
| Arthralgia | 1 (1.9) | 0 |
| Arthritis | 1 (1.9) | 0 |
| Muscle spasms | 0 | 1 (2.0) |
| Scoliosis | 1 (1.9) | 0 |
| Neoplasms Benign, Malignant and Unspecified (including cysts and polyps) | 2 (3.8) | 1 (2.0) |
| Skin papilloma | 2 (3.8) | 1 (2.0) |
| Nervous System Disorders | 2 (3.8) | 4 (8.0) |
| Headache | 2 (3.8) | 1 (2.0) |
| Hypoaesthesia | 0 | 1 (2.0) |
| Paraesthesia | 1 (1.9) | 1 (2.0) |
| Restless legs syndrome | 0 | 1 (2.0) |
| Respiratory, Thoracic and Mediastinal Disorders | 5 (9.6) | 2 (4.0) |
| Asthma | 1 (1.9) | 0 |
| Cough | 4 (7.7) | 1 (2.0) |
| Dyspnoea | 1 (1.9) | 0 |
| Oropharyngeal pain | 3 (5.8) | 1 (2.0) |
| Rhinorrhoea | 0 | 1 (2.0) |
| Sinus congestion | 1 (1.9) | 0 |
| Skin and Subcutaneous Tissue Disorders | 8 (15.4) | 2 (4.0) |
| Acne | 1 (1.9) | 0 |
| Alopecia | 1 (1.9) | 0 |
| Dry skin | 1 (1.9) | 0 |
| Erythema | 1 (1.9) | 0 |
| Ingrowing nail | 1 (1.9) | 0 |
| Leukoplakia | 1 (1.9) | 0 |
| Photosensitivity allergic reaction | 1 (1.9) | 0 |
| Post inflammatory pigmentation change | 1 (1.9) | 0 |
| Psoriasis | 1 (1.9) | 0 |

| System Organ Class (SOC) | High-Dose 40 mg eow N = 52 n (%) | Low-Dose 20 mg eow N = 50 n (%) |
|--------------------------|---|--|
| Rash | 1 (1.9) | 1 (2.0) |
| Rash erythematous | 2 (3.8) | 0 |
| Rash papular | 1 (1.9) | 0 |
| Skin fissures | 1 (1.9) | 0 |
| Skin reaction | 0 | 1 (2.0) |
| Urticaria | 1 (1.9) | 0 |

Definition: eow = every other week

All treatment-emergent serious adverse events were observed in 21% (11/52) of patients receiving High-Dose and 20% (10/50) of patients receiving Low-Dose. Serious infections were observed in 6% (3/52) of patients receiving High-Dose and 2% (1/50) of patients receiving Low-Dose. The serious adverse events in the High-Dose group included anemia, Crohn's disease, anal abscess, gastroenteritis, and histoplasmosis disseminated. The serious adverse events in the Low-Dose group included Crohn's disease, pancreatitis acute, Bartholin's abscess, and facial bones fracture.

A total of 56% (29/52) of patients receiving High-Dose and 52% (26/50) of patients receiving Low-Dose experienced an infection (see also **WARNINGS AND PRECAUTIONS [8], Infections**). Overall adverse events were observed in 96% (50/52) of patients receiving High-Dose and 86% (43/50) of patients receiving Low-Dose.

Adolescent Hidradenitis Suppurativa

There are no clinical trials conducted to evaluate the safety of adalimumab in adolescents with hidradenitis suppurativa.

Pediatric Uveitis

[Table 16](#) summarizes adverse drug reactions reported in the SYCAMORE study at a rate of at least 1% in the indicated pediatric patient population with active JIA-associated chronic non-infectious anterior uveitis treated with adalimumab in combination with MTX.

Table 16 Number and Percentage of Patients with \geq 1% Treatment-Emergent Adverse Events at Least Possibly Related to Study Drug in the SYCAMORE Pediatric Uveitis Study

| System Organ Class (SOC) | Adalimumab N = 60 n (%) | Placebo N = 30 n (%) |
|---|--|-------------------------------------|
| Blood and Lymphatic System Disorders | 4 (6.7) | 0 |
| Lymphadenopathy | 3 (5.0) | 0 |
| Neutropenia | 1 (1.7) | 0 |
| Eye Disorders | 4 (6.7) | 4 (13.3) |
| Anterior chamber flare | 0 | 1 (3.3) |
| Dry eye | 1 (1.7) | 0 |
| Eye inflammation | 1 (1.7) | 0 |
| Eye pain | 1 (1.7) | 0 |
| Uveitis | 0 | 3 (10.0) |
| Visual impairment | 1 (1.7) | 0 |
| Gastrointestinal Disorders | 10 (16.7) | 2 (6.7) |
| Abdominal pain | 1 (1.7) | 0 |
| Diarrhoea | 4 (6.7) | 0 |
| Food poisoning | 1 (1.7) | 0 |
| Nausea | 2 (3.3) | 0 |
| Vomiting | 7 (11.7) | 2 (6.7) |
| General Disorders and Administration Site Conditions | 23 (38.3) | 5 (16.7) |
| Chest discomfort | 1 (1.7) | 0 |
| Fatigue | 0 | 1 (3.3) |
| Influenza like illness | 1 (1.7) | 0 |
| Injection site erythema | 3 (5.0) | 1 (3.3) |
| Injection site mass | 2 (3.3) | 0 |
| Injection site pain | 5 (8.3) | 2 (6.7) |
| Injection site pruritus | 3 (5.0) | 0 |
| Injection site reaction | 6 (10.0) | 0 |
| Injection site swelling | 3 (5.0) | 1 (3.3) |
| Injection site vesicles | 1 (1.7) | 0 |
| Malaise | 1 (1.7) | 0 |
| Pyrexia | 8 (13.3) | 1 (3.3) |
| Swelling | 1 (1.7) | 0 |

| System Organ Class (SOC) | Adalimumab N = 60 n (%) | Placebo N = 30 n (%) |
|---|--|-------------------------------------|
| Infections and Infestations | 32 (53.3) | 8 (26.7) |
| Candida infection | 1 (1.7) | 0 |
| Cellulitis | 1 (1.7) | 0 |
| Conjunctivitis viral | 1 (1.7) | 0 |
| Ear infection | 3 (5.0) | 2 (6.7) |
| Eye infection | 1 (1.7) | 0 |
| Herpes simplex | 1 (1.7) | 0 |
| Herpes zoster | 0 | 1 (3.3) |
| Impetigo | 3 (5.0) | 1 (3.3) |
| Infected bites | 1 (1.7) | 0 |
| Infection | 1 (1.7) | 0 |
| Localised infection | 0 | 1 (3.3) |
| Lower respiratory tract infection | 8 (13.3) | 2 (6.7) |
| Molluscum contagiosum | 2 (3.3) | 0 |
| Nasopharyngitis | 6 (10.0) | 2 (6.7) |
| Oral herpes | 2 (3.3) | 1 (3.3) |
| Paronychia | 2 (3.3) | 1 (3.3) |
| Pharyngitis | 2 (3.3) | 0 |
| Pneumonia | 1 (1.7) | 0 |
| Rhinitis | 1 (1.7) | 0 |
| Scarlet fever | 1 (1.7) | 0 |
| Skin infection | 2 (3.3) | 0 |
| Staphylococcal infection | 1 (1.7) | 0 |
| Streptococcal infection | 1 (1.7) | 0 |
| Tonsillitis | 10 (16.7) | 0 |
| Upper respiratory tract infection | 3 (5.0) | 1 (3.3) |
| Urethritis | 0 | 1 (3.3) |
| Urinary tract infection | 6 (10.0) | 2 (6.7) |
| Varicella | 1 (1.7) | 0 |
| Viral infection | 8 (13.3) | 1 (3.3) |
| Injury, Poisoning and Procedural Complications | 1 (1.7) | 0 |
| Contusion | 1 (1.7) | 0 |

| System Organ Class (SOC) | Adalimumab N = 60 n (%) | Placebo N = 30 n (%) |
|---|--|-------------------------------------|
| Investigations | 6 (10.0) | 1 (3.3) |
| Alanine aminotransferase increased | 3 (5.0) | 0 |
| Aspartate aminotransferase increased | 2 (3.3) | 0 |
| Blood alkaline phosphatase increased | 1 (1.7) | 0 |
| Liver function test abnormal | 1 (1.7) | 0 |
| Neutrophil count decreased | 0 | 1 (3.3) |
| Red blood cell sedimentation rate abnormal | 1 (1.7) | 0 |
| Rubulavirus test positive | 1 (1.7) | 0 |
| Metabolism and Nutrition Disorders | 3 (5.0) | 0 |
| Decreased appetite | 2 (3.3) | 0 |
| Dehydration | 1 (1.7) | 0 |
| Musculoskeletal and Connective Tissue Disorders | 5 (8.3) | 1 (3.3) |
| Arthralgia | 3 (5.0) | 1 (3.3) |
| Arthritis | 1 (1.7) | 0 |
| Joint stiffness | 1 (1.7) | 0 |
| Pain in extremity | 1 (1.7) | 0 |
| Neoplasms Benign, Malignant and Unspecified (including cysts and polyps) | 4 (6.7) | 0 |
| Skin papilloma | 4 (6.7) | 0 |
| Nervous System Disorders | 5 (8.3) | 1 (3.3) |
| Headache | 5 (8.3) | 1 (3.3) |
| Reproductive System and Breast Disorders | 1 (1.7) | 0 |
| Pruritus genital | 1 (1.7) | 0 |

| System Organ Class (SOC) | Adalimumab N = 60 n (%) | Placebo N = 30 n (%) |
|--|-------------------------------|----------------------------|
| Respiratory, Thoracic and Mediastinal Disorders | 12 (20.0) | 2 (6.7) |
| Cough | 9 (15.0) | 2 (6.7) |
| Nasal discomfort | 2 (3.3) | 0 |
| Oropharyngeal pain | 8 (13.3) | 0 |
| Productive cough | 1 (1.7) | 0 |
| Snoring | 1 (1.7) | 0 |
| Tonsillar hypertrophy | 1 (1.7) | 0 |
| Skin and Subcutaneous Tissue Disorders | 3 (5.0) | 2 (6.7) |
| Dermatitis | 0 | 1 (3.3) |
| Erythema | 1 (1.7) | 0 |
| Ingrowing nail | 1 (1.7) | 0 |
| Rash | 1 (1.7) | 1 (3.3) |

In the SYCAMORE study, adalimumab was studied in 90 pediatric patients (randomized 2:1 to adalimumab:placebo) with active JIA-associated chronic non-infectious anterior uveitis. Overall, serious adverse events were observed in 22% of patients treated with adalimumab in combination with MTX and included varicella, streptococcal infections, viral infection, diarrhea, syncope, scarlet fever, cellulitis, infected bites, lower respiratory tract infection, cataract, testes exploration, antiviral prophylaxis, food poisoning, and tonsillar hypertrophy. Serious infections were observed in 13% of patients with adalimumab. Serious adverse events were more frequent in children 4 years of age and younger.

9.6 Post-Market Adverse Reactions

The following post-market adverse drug reactions have been reported:

| | |
|---|--|
| Cardiac Disorders: | myocardial infarction |
| Gastrointestinal Disorders: | diverticulitis, intestinal perforation, pancreatitis |
| General disorders and administration site conditions: | pyrexia |
| Hematologic Events: | thrombocytopenia [†] |
| Hepatobiliary Disorders: | liver failure, hepatitis, autoimmune hepatitis |
| Hypersensitivity Reactions: | anaphylaxis [†] , angioedema, angioneurotic edema |
| Immune System Disorders: | Sarcoidosis |

| | |
|--|--|
| Infections: | infections in infants exposed in utero, legionellosis, listeriosis, reactivation of hepatitis B virus (HBV) † |
| Musculoskeletal and Connective Tissue Disorders: | lupus-like syndrome†* |
| Neoplasia: | hepatosplenic T-cell lymphoma (HSTCL) †, leukemia†, Merkel cell carcinoma (neuroendocrine carcinoma of the skin) |
| Nervous System Disorders: | cerebrovascular accident, demyelinating disorders (eg, Guillain-Barré syndrome, optic neuritis) |
| Skin Reactions: | alopecia, cutaneous vasculitis, erythema multiforme, lichenoid skin reaction**, new onset or worsening of psoriasis (including palmoplantar pustular psoriasis)*, Stevens-Johnson syndrome |
| Respiratory, Thoracic and Mediastinal Disorders: | interstitial lung disease (including pulmonary fibrosis), pulmonary embolism |
| Vascular Disorders: | deep vein thrombosis, systemic vasculitis |

† (See **WARNINGS AND PRECAUTIONS [8]**)

* (See **Adverse Drug Reaction Overview [9.1]**)

** occurring in patients receiving a TNF-antagonist including adalimumab

10 DRUG INTERACTIONS

10.1 Serious Drug Interactions Box

Serious Drug Interactions

Serious infections and sepsis, including fatalities, have been reported with the use of TNF-blocking agents, including adalimumab. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their rheumatoid arthritis, could predispose them to infections. Tuberculosis and invasive opportunistic fungal infections have been observed in patients treated with TNF-blocking agents, including adalimumab.

10.2 Overview

Population pharmacokinetic analyses with data from over 1,200 rheumatoid arthritis patients revealed that co-administration of MTX had an intrinsic effect on the apparent clearance of adalimumab (CL/F). (See **Drug-Drug Interactions [10.3]**). As expected, there was a trend toward higher apparent clearance of adalimumab with increasing body weight and in the presence of anti-adalimumab antibodies.

Other more minor factors were also identified: higher apparent clearance was predicted in rheumatoid arthritis patients receiving doses lower than the recommended dose, and in rheumatoid arthritis patients with high rheumatoid factor or C-reactive protein (CRP) concentrations. These factors are not likely to be clinically important.

AMGEVITA and adalimumab have been studied in rheumatoid arthritis patients taking concomitant MTX. (See **COMPARATIVE CLINICAL TRIALS [15]** and **CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG [17]**). The data do not suggest the need for dose adjustment of either AMGEVITA or MTX.

10.3 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

| Concomitant Drug Name | Clinical Comment |
|-------------------------------------|---|
| Abatacept | Concurrent administration of TNF-blockers and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-blockers alone. This combination has not demonstrated increased clinical benefit. Thus the combined use of TNF-blockers and abatacept is not recommended. |
| Anakinra | Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent has been associated with an increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared to these medicinal products alone. Therefore, the combination of anakinra with other TNF-blocking agents, including AMGEVITA, may also result in similar toxicities. (See WARNINGS AND PRECAUTIONS [8], General, Concurrent Administration of Biologic DMARDs or TNF-antagonists). |
| Cytochrome P450 (CYP450) Substrates | The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (eg, TNF α , IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of AMGEVITA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (eg, warfarin) or drug concentration (eg, cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed. |
| Methotrexate (MTX) | When adalimumab was administered to 21 rheumatoid arthritis patients on stable MTX therapy, there were no statistically significant changes in the serum MTX concentration profiles. In contrast, after single and multiple dosing, MTX reduced adalimumab, the reference biologic drug, apparent clearances by 29 and 44% respectively, in patients with rheumatoid arthritis. (See CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG [17]). |
| Other | Interactions between adalimumab and drugs other than MTX have not been evaluated in formal pharmacokinetic studies. In rheumatoid arthritis clinical trials where adalimumab was co-administered with commonly-used DMARDs (sulfasalazine, hydrochloroquine, leflunomide and parenteral gold), glucocorticoids, salicylates, NSAIDs or analgesics, no safety signals were seen. There is no data on other DMARDs, and patients with prior treatment with alkylating agents (eg, cyclophosphamide) were excluded. |

Definition(s): DMARDs = disease-modifying anti-rheumatic drugs; MTX = methotrexate; TNF = tumour necrosis factor

10.4 Drug-Food Interactions

AMGEVITA is administered as a subcutaneous injection. Interactions with food are therefore not applicable.

10.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

10.6 Drug-Laboratory Test Interactions

There are no known laboratory tests that may be helpful in following the patient's response or in identifying possible adverse reactions

10.7 Drug-Lifestyle Interactions

AMGEVITA may have a minor influence on the ability to drive and use machines. Dizziness (including vertigo, vision disorder and fatigue) may occur following administration of AMGEVITA.

11 ACTION AND CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF-expressing cells *in vitro* in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally-occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of rheumatoid arthritis, including polyarticular JIA, psoriatic arthritis and ankylosing spondylitis patients and play an important role in both pathologic inflammation and joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques, which contribute to the inflammatory response, to the proliferation and decreased maturation of keratinocytes and to the associated vascular damages that are characteristic of the disease. Increased levels of TNF are also found in hidradenitis suppurativa lesions.

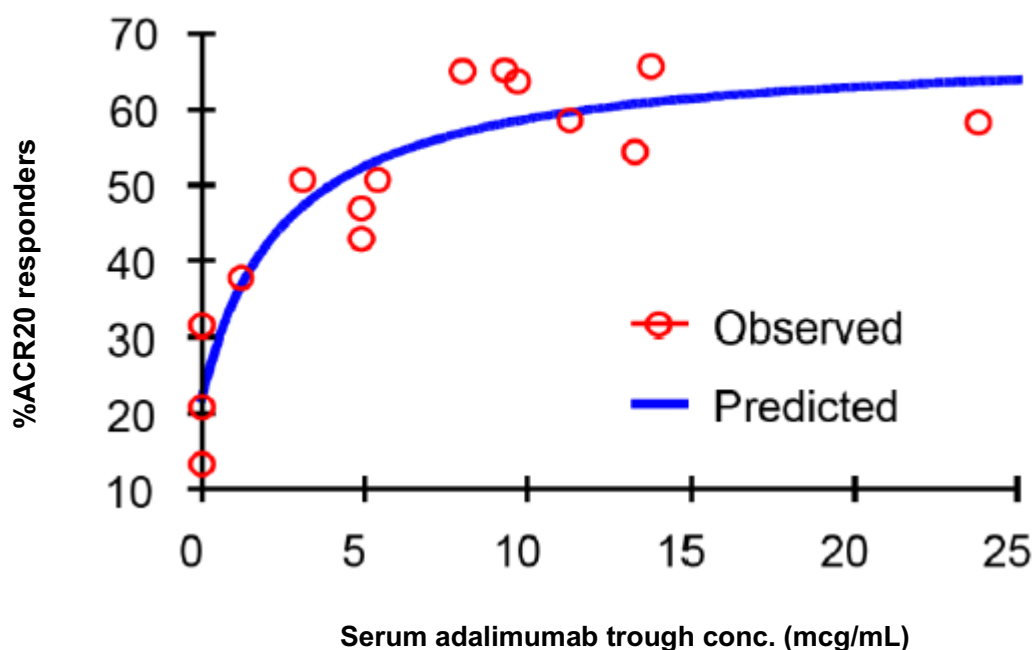
Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration [ELAM-1, VCAM-1, and ICAM-1 with a half maximal inhibitory concentration (IC₅₀) of 1 to 2 x 10⁻¹⁰M for adalimumab, the reference biologic drug].

11.2 Pharmacodynamics

After treatment with adalimumab, a rapid decrease in levels of acute phase reactants of inflammation [CRP and erythrocyte sedimentation rate (ESR)] and serum cytokines (IL-6) was observed compared to baseline in patients with rheumatoid arthritis. A rapid decrease in CRP levels was also observed in patients with Crohn's disease, ulcerative colitis and hidradenitis suppurativa. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after adalimumab administration.

The serum adalimumab concentration-efficacy relationship as measured by the American College of Rheumatology response criteria (ACR 20) appears to follow the Hill E_{max} equation as shown in [Figure 1](#).

Figure 1. Serum Adalimumab Concentration-Efficacy Relationship as Measured by the American College of Rheumatology Response Criteria (ACR 20)



The half maximal effective concentration (EC_{50}) estimates ranging from 0.8 to 1.4 mcg/mL were obtained through pharmacokinetic / pharmacodynamic modelling of swollen joint count, tender joint count and ACR 20 response from patients participating in Phase 2 and 3 trials of adalimumab.

11.3 Pharmacokinetics

Pediatrics

Following the administration of 24 mg/m² (up to a maximum of 40 mg) subcutaneously every other week to patients with polyarticular JIA who were 4 to 17 years, the mean trough steady-state (values measured from Week 20 to 48) serum adalimumab concentration was 5.5 ± 5.6 mcg/mL [102% coefficient of variation (CV)] adalimumab monotherapy and 10.9 ± 5.2 mcg/mL (47.7% CV) with concomitant MTX. In patients with polyarticular JIA who were 2 to < 4 years old or aged 4 and above weighing < 15 kg dosed with adalimumab 2 mg/m², the mean trough steady-state serum adalimumab concentrations was 6.0 ± 6.1 µg/mL (101% CV) adalimumab monotherapy and 7.9 ± 5.6 µg/mL (71.2% CV) with concomitant MTX.

In pediatric patients 13 to 17 years of age weighing ≥ 40 kg with severely active Crohn's disease and/or who have had an inadequate response or were intolerant to conventional therapy, the mean ± SD serum adalimumab trough concentration achieved at Week 4 was 15.7 ± 6.64 mcg/mL following administration of 160 mg adalimumab at Week 0 and 80 mg adalimumab at Week 2. The mean ± SD adalimumab trough concentrations at Week 4 were 17.2 ± 6.67 mcg/mL (n = 45) for patients who were naïve to infliximab. The mean ± SD adalimumab trough concentrations at Week 4 were 14.4 ± 6.40 mcg/mL (n = 51) for patients who were infliximab-experienced.

For patients who stayed on their randomized double-blind therapy, the mean ± SD adalimumab, trough concentration at Week 52 was 9.43 ± 4.98 mcg/mL following administration of 40 mg

adalimumab every other week and 3.59 ± 2.91 mcg/mL following administration of 20 mg adalimumab every other week. For patients who stayed on their randomized double-blind therapy and were naïve to infliximab, the mean \pm SD adalimumab trough concentrations at Week 52 were 12.0 ± 3.89 mcg/mL ($n = 11$) and 3.06 ± 2.02 mcg/mL ($n = 10$) for the High-Dose and Low-Dose groups, respectively. For patients who stayed on their randomized double-blind therapy and were infliximab-experienced, the mean \pm SD adalimumab trough concentrations at Week 52 were 6.85 ± 4.72 mcg/mL ($n = 11$) and 4.27 ± 2.82 mcg/mL ($n = 8$) for the High-Dose and Low-Dose groups, respectively.

Adalimumab exposure in adolescent hidradenitis suppurativa patients was predicted using population pharmacokinetic modeling and simulation based on cross-indication pharmacokinetics in other pediatric patients (pediatric psoriasis, JIA, pediatric Crohn's disease, and enthesitis-related arthritis). Serum adalimumab concentrations in adolescent patients with hidradenitis suppurativa receiving the recommended dosage regimen are predicted to be similar to those observed in adult subjects with hidradenitis suppurativa (steady-state trough concentration of approximately 8 to 10 mcg/mL).

Adalimumab exposure in pediatric uveitis patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other pediatric patients ($N = 524$) (pediatric psoriasis [age 5 to 18 years, $n = 109$], JIA [age 2 to 17 years, $n = 181$], pediatric Crohn's disease [age 6 to 17 years, $n = 189$], and enthesitis-related arthritis [age 6 to 18 years, $n = 45$]). No clinical exposure data are available on the use of a loading dose in children < 6 years. The predicted exposures indicate that in the absence of methotrexate, a loading dose may lead to an initial increase in systemic exposure.

Adult

The single-dose pharmacokinetics of adalimumab in rheumatoid arthritis patients were determined in several studies with intravenous doses ranging from 0.25 to 10.0 mg/kg. The distribution volume (V_{ss}) ranged from 4.7 to 6.0 L. The systemic clearance of adalimumab is approximately 12 mL/h. The mean terminal half-life was approximately two weeks, ranging from 10 to 20 days across studies. The pharmacokinetics of adalimumab were linear over the dose range of 0.5 to 10.0 mg/kg following a single intravenous dose.

Adalimumab mean steady-state trough concentrations of approximately 5 mcg/mL and 8 to 9 mcg/mL, were observed in rheumatoid arthritis patients without and with MTX, respectively. The serum adalimumab trough levels at steady-state increased approximately proportionally with dose following 20, 40 and 80 mg every other week and every week subcutaneous dosing. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time.

Population pharmacokinetic analyses in patients with rheumatoid arthritis revealed that there was a trend toward higher apparent clearance of adalimumab in the presence of anti-adalimumab antibodies.

In patients with psoriatic arthritis, adalimumab mean steady-state trough concentrations of 8.5 to 12 mcg/mL and 6 to 10 mcg/mL were observed in patients with and without MTX, respectively.

In patients with Crohn's disease, the loading dose of 160 mg adalimumab on Week 0 followed by 80 mg adalimumab on Week 2 achieves mean serum adalimumab trough concentrations of approximately 12 mcg/mL at Week 2 and Week 4. Mean steady-state trough levels of approximately 7 mcg/mL were observed at Week 24 and Week 56 in Crohn's disease patients who received a maintenance dose of adalimumab 40 mg every other week.

Population pharmacokinetic analysis in patients with Crohn's disease revealed a lower apparent clearance of adalimumab as compared to patients with rheumatoid arthritis.

In patients with ulcerative colitis, a loading dose of 160 mg adalimumab on Week 0 followed by 80 mg adalimumab on Week 2 achieved serum adalimumab trough concentrations of 11.8 ± 4.0 mcg/mL at Week 2 (n = 167) and 12.3 ± 5.4 mcg/mL at Week 4 (n = 160). At Week 52, trough levels of 8.0 ± 6.1 mcg/mL were observed in ulcerative colitis patients who received a maintenance dose of 40 mg adalimumab every other week (n = 101). Trough levels at Week 52 were 10.8 ± 7.5 mcg/mL in ulcerative colitis patients achieving remission (n = 39) and 6.2 ± 4.2 mcg/mL in ulcerative colitis patients not achieving remission (n = 62).

In patients with hidradenitis suppurativa, a dose of 160 mg adalimumab on Week 0 followed by 80 mg adalimumab on Week 2 achieved serum adalimumab trough concentrations of approximately 7 to 8 mcg/mL at Week 2 and Week 4. The mean steady-state trough concentration at Week 12 through Week 36 were approximately 8 to 10 mcg/mL during adalimumab 40 mg every week treatment.

In patients with psoriasis, the mean steady-state trough concentration was 5 mcg/mL during adalimumab 40 mg every other week monotherapy treatment.

In patients with uveitis, a loading dose of 80 mg adalimumab on Week 0 followed by 40 mg adalimumab every other week starting at Week 1, resulted in mean steady-state concentrations of approximately 8 to 10 mcg/mL.

Absorption: The maximum serum concentration (C_{max}) and the time to reach the maximum concentration (T_{max}) were 4.7 ± 1.6 mcg/mL and 131 ± 56 hours respectively, following a single 40 mg subcutaneous administration of adalimumab to healthy adult subjects. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. The pharmacokinetics of adalimumab were linear over the dose range of 0.5 to 10.0 mg/kg following a single intravenous dose.

Distribution: Adalimumab concentrations in the synovial fluid from five rheumatoid arthritis patients ranged from 31 to 96% of those in serum.

Metabolism: No formal studies have been conducted to evaluate the metabolism of adalimumab. However, as adalimumab is an IgG1 antibody of entirely human sequences, it is expected that its metabolism would follow the course of other IgG molecules.

Elimination: No formal studies have been conducted to evaluate the excretion of adalimumab. However, as adalimumab is an IgG1 antibody of entirely human sequences, it is expected that its excretion would follow the course of other IgG molecules.

11.4 Special Populations and Conditions

Pediatrics:

Adalimumab has not been studied in pediatric patients with polyarticular JIA less than 2 years of age or in patients with a weight < 10 kg.

The majority (102/192) of pediatric patients with Crohn's disease studied were 13 to 17 years of age weighing ≥ 40 kg.

There are no clinical trials with adalimumab in adolescent patients (12 to 17 years of age) with hidradenitis suppurativa. Use of adalimumab in adolescent patients is supported by evidence from adequate and well-controlled studies of adalimumab in adult hidradenitis suppurativa patients with supplemental pharmacokinetic modeling and simulation. The use of adalimumab has not been established in patients younger than 12 years of age with hidradenitis suppurativa.

Adalimumab has not been studied in pediatric patients with uveitis less than 2 years of age. Very limited data are available for pediatric patients with uveitis between 2 and < 3 years of age.

Geriatrics:

Population pharmacokinetic analyses in patients with rheumatoid arthritis revealed that there was a trend toward lower clearance with increasing age in patients aged 40 to > 75 years of age.

Sex:

Population pharmacokinetic analyses in patients with rheumatoid arthritis revealed that no gender-related pharmacokinetic differences were observed after correction for a patient's body weight.

Ethnic origin:

No differences in immunoglobulin clearance would be expected among races. From limited data in non-Caucasians, no important kinetic differences were observed for adalimumab.

Hepatic Insufficiency:

No pharmacokinetic data are available in patients with hepatic impairment.

Renal Insufficiency:

No pharmacokinetic data are available in patients with renal impairment.

Disease States:

Healthy volunteers and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics. Population pharmacokinetic analyses predicted minor increases in apparent clearance in patients receiving doses lower than the recommended dose and in patients with high rheumatoid factor or C-reactive protein (CRP) concentrations. These increases are not likely to be clinically important. (See **Dosing Considerations [4.1]**, **Disease States**).

12 STORAGE, STABILITY AND DISPOSAL

Do not use beyond the expiration date on the container. AMGEVITA must be refrigerated at 2°C to 8°C. DO NOT FREEZE. Do not use if frozen even if it has been thawed.

Store in original carton until time of administration to protect from light.

If needed, for example when traveling, AMGEVITA may be stored at room temperature up to a maximum of 25°C for a period of up to 14 days, with protection from light.

AMGEVITA should be discarded if not used within the 14-day period. Record the date when AMGEVITA is first removed from the refrigerator in the spaces provided on the carton.

Do not store AMGEVITA in extreme heat or cold.

13 SPECIAL HANDLING INSTRUCTIONS

The needle cap on the prefilled syringe and cap containing a needle cover on the prefilled autoinjector contains dry natural rubber (a derivative of latex) that may cause allergic reactions in individuals sensitive to latex.

A puncture-resistant container for disposal of needles, syringes, and autoinjectors should be used. Patients and caregivers should be instructed in the technique of proper syringe and needle disposal, and be cautioned against reuse of these items.

PART II: SCIENTIFIC INFORMATION

14 PHARMACEUTICAL INFORMATION

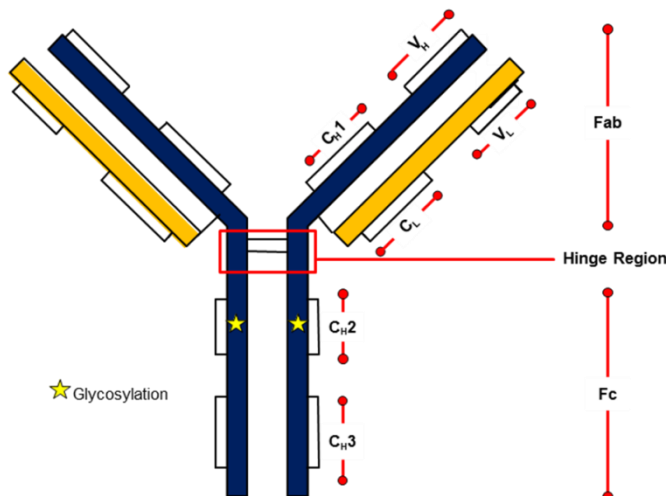
Drug Substance

Proper name: adalimumab

Chemical name: anti-tumour necrosis factor (TNF) alpha monoclonal antibody

Molecular formula and molecular mass: AMGEVITA (adalimumab) contains 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. The amino acid sequence of AMGEVITA (adalimumab) is identical to that of HUMIRA® (adalimumab reference biologic drug).

Structural formula: AMGEVITA consists of 2 heavy chains of the IgG1 subclass and 2 light chains of the human kappa subclass, which are covalently linked through disulfide bonds. It contains 1330 amino acids and has a molecular weight of approximately 148 kilodaltons.



Heavy chains are shown in blue and light chains are shown in orange.
Black lines represent disulfide bonds.
V_H is the variable domain of the heavy chain.
C_H1, C_H2, and C_H3 are the constant domains of the heavy chain.
V_L is the variable domain of the light chain.
C_L is the constant domain of the light chain.

Physicochemical properties: AMGEVITA is a clear, colourless to slightly yellow, sterile preservative free solution with a pH of 5.2.

Product Characteristics

AMGEVITA is a fully human anti-TNF α monoclonal antibody expressed in a Chinese hamster ovary (CHO) cell line. AMGEVITA is produced by recombinant DNA technology in a mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps.

15 COMPARATIVE CLINICAL TRIALS

15.1 Comparative Trial Design and Study Demographics

Clinical studies conducted to support similarity between AMGEVITA and the reference biologic drug included:

- A pivotal comparative pharmacokinetic (PK) phase I study in healthy volunteers
- A pivotal comparative efficacy and safety study in combination with methotrexate (MTX) in patients with moderate to severely active rheumatoid arthritis
- A pivotal comparative efficacy and safety study in patients with moderate to severely active plaque psoriasis

An overview of the study design(s) and patient demographics for each clinical study are presented in [Table 17](#).

Table 17 Summary of Trial Design and Patient Demographics

| Study # | Trial design and study objective(s) | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex (% female) |
|---------------------------------------|---|--|--------------------|------------------|----------------|
| 20110217 PK similarity | Phase 1 randomized, single-blind, single-dose, 3 arm, parallel group PK similarity, safety, tolerability, immunogenicity and bridging between HUMIRA® (US) and HUMIRA® (EU) in healthy subjects | AMGEVITA 40 mg, | 67 | 29.3 (19-45) | 50.7% |
| | | HUMIRA® (US) 40 mg | 69 | 28.7 (19-45) | 44.9% |
| | | HUMIRA® (EU) 40 mg | 67 | 27.8 (18-44) | 32.8% |
| | | Subcutaneous Single dose | | | |
| 20120262 Efficacy and Safety | Phase 3 randomized, double-blind, active comparator controlled Efficacy, safety, immunogenicity, PK in patients with moderate to severe RA for ≥ 3 months | AMGEVITA 40 mg, eow | 264 | 55.4 (22-80) | 81.1% |
| | | HUMIRA® (US) 40 mg, eow | 262 | 56.3 (21-77) | 80.9% |
| | | Subcutaneous 26 weeks | | | |

| Study # | Trial design and study objective(s) | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex (% female) |
|---------------------------------|--|---|--------------------|------------------|----------------|
| 20120263 Efficacy and Safety | Phase 3, randomized, double-blind, active comparator-controlled Efficacy, safety, immunogenicity, PK in patients with moderate to severe Ps for ≥ 6 months Subjects qualifying for re-randomization at week 16: AMGEVITA group continued treatment with AMGEVITA; Adalimumab group re-randomized to adalimumab or AMGEVITA | AMGEVITA 80 mg week 1/day 1, then 40 mg eow beginning at week 2 | 175 | 45.1 (18-74) | 36.0% |
| | | HUMIRA® (EU) 80 mg week 1/day 1, then 40 mg eow beginning at week 2 Subcutaneous 52 weeks | 175 | 44.0 (18-73) | 33.7% |

Definition(s): eow = every other week; EU = European Union; PK = pharmacokinetic; Ps = plaque psoriasis; RA = rheumatoid arthritis; SC = subcutaneous; US = United States.

15.2 Comparative Study Results

15.2.1 Comparative Bioavailability Studies

15.2.1.1 Pharmacokinetics

Comparative Pharmacokinetic Study 20110217

This was a randomized, single-blind, single-dose, 3-arm, parallel group study in healthy adult subjects. The primary objective of this study was to demonstrate the PK similarity of AMGEVITA to HUMIRA® [United States (US)] and to HUMIRA® [European Union (EU)] assessed by the PK parameters AUC_{inf} and C_{max} .

In Study 20110217, 203 healthy adult subjects were enrolled and randomized (in a 1:1:1 ratio) to treatment with AMGEVITA, HUMIRA® (US), or HUMIRA® (EU). Subjects received a single 40 mg subcutaneous (SC) dose of AMGEVITA, HUMIRA® (US), or HUMIRA® (EU) on day 1 and returned periodically for safety evaluations [including antidrug antibody (ADA) levels] and PK sample collections until day 63.

Study Results

When comparing PK parameters of AMGEVITA versus HUMIRA® (US) and of AMGEVITA versus HUMIRA® (EU) following a single 40 mg SC injection, the 90% confidence intervals (CIs) of the ratios of the geometric means for C_{max} , AUC_{last} , and AUC_{inf} were fully contained within the pre-defined bounds of 80% to 125%. The ratio of the geometric means for the AUC_{inf} of AMGEVITA versus HUMIRA® (US) was 111% (100%, 124%) and AMGEVITA versus HUMIRA® (EU) was 104% (93.5%, 117%). In addition, when comparing PK parameters of HUMIRA® (US) versus HUMIRA® (EU), the 90% CIs of the ratios of the geometric means for all 3 parameters were fully contained within the pre-defined bounds of 80% to 125%.

The statistical assessments of the pharmacokinetic parameters for AMGEVITA, HUMIRA® (US) and HUMIRA® (EU) are shown in Table 18 and Table 19.

Table 18 AMGEVITA and HUMIRA® (US) Pharmacokinetic Parameters (Study 20110217)

| Parameter | AMGEVITA | HUMIRA® (US) | Ratio of Geometric LS Means | 90% Confidence Interval |
|--|--------------------------|--------------------------|-----------------------------|-------------------------|
| AUC _{last} (µg.h/mL) Geometric LS Mean [n] | 2000 [67] | 1880 [69] | 1.07 | 0.964, 1.18 |
| AUC _{inf} (µg.h/mL) Geometric LS Mean [n] | 2140 [58] | 1920 [61] | 1.11 | 1.00, 1.24 |
| C _{max} (µg/mL) Geometric LS Mean [n] | 3.22 [67] | 3.11 [69] | 1.04 | 0.964, 1.12 |
| T _{max} (h) Median [n] (Min - Max) | 191 [67] (47.2 - 360) | 144 [69] (47.0 - 359) | | |
| T _½ (h) Mean [n] (SD) | 246 [58] (160) | 215 [61] (121) | | |

Definition(s): AUC_{last} = area under the concentration-time curve from time 0 to the last quantifiable concentration; C_{max} = maximum serum concentration; LS = least squares; max = maximum; min = minimum; n = number of non-missing observations; SD = standard deviation; US = United States.

Table 19 AMGEVITA and HUMIRA® (EU) Pharmacokinetic Parameters (Study 20110217)

| Parameter | AMGEVITA | HUMIRA® (EU) | Ratio of Geometric LS Means | 90% Confidence Interval |
|--|--------------------------|--------------------------|-----------------------------|-------------------------|
| AUC _{last} (µg.h/mL) Geometric LS Mean [n] | 2000 [67] | 2020 [66] | 0.99 | 0.892, 1.10 |
| AUC _{inf} (µg.h/mL) Geometric LS Mean [n] | 2140 [58] | 2050 [57] | 1.04 | 0.935, 1.17 |
| C _{max} (µg/mL) Geometric LS Mean [n] | 3.22 [67] | 3.37 [67] | 0.96 | 0.889, 1.03 |
| T _{max} (h) Median [n] (Min - Max) | 191 [67] (47.2 - 360) | 168 [67] (48.0 - 313) | | |
| T _½ (h) Mean [n] (SD) | 246 [58] (160) | 233 [57] (151) | | |

Definition(s): AUC_{last} = area under the concentration-time curve from time 0 to the last quantifiable concentration; C_{max} = maximum serum concentration; EU = European Union; LS = least squares; max = maximum; min = minimum; n = number of non-missing observations; SD = standard deviation.

15.2.2 Comparative Safety and Efficacy

15.2.2.1 Efficacy

Rheumatoid Arthritis

Study 20120262, a randomized, double-blind, active comparator-controlled study in adult subjects with moderate to severe rheumatoid arthritis who had an inadequate response to MTX evaluated the efficacy of AMGEVITA compared with HUMIRA® as the primary objective.

All subjects received a stable dose of MTX concomitantly with AMGEVITA or HUMIRA® and were to be naïve to adalimumab.

Patients had rheumatoid arthritis for at least 3 months duration and at least 6 swollen and 6 tender joints and high erythrocyte sedimentation rate [ESR (≥ 28 mm/h)] or serum C-reactive protein [CRP (> 1.0 mg/dL)] at the study entry. The patients had either rheumatoid factor or anti-cyclic citrullinated peptide positivity. The study evaluated 526 patients who had an inadequate response to MTX at doses of 7.5 to 25 mg. Patients received 40 mg of AMGEVITA or HUMIRA® (US) subcutaneously every other week for up to 22 weeks.

Efficacy measures included the composite scores of American College of Rheumatology (ACR) responses and change from baseline in Disease Activity Score 28 C-reactive protein (DAS28 CRP), both widely accepted as measures of disease activity and, therefore, appropriate to demonstrate similarity of efficacy in the rheumatoid arthritis population. The primary efficacy endpoint of this study was the risk ratio of 20% improvement in ACR core set measurements (ACR20) assessed at week 24 with missing response imputed by Last Observation Carried Forward (LOCF) with sensitivity analysis by Non-responder Imputation (NRI).

Secondary efficacy endpoints included risk ratio of ACR20 response at time points earlier than week 24, risk difference of ACR20 response at each time point, DAS28-CRP change from baseline at each time point, and risk ratio and risk difference of ACR50 and ACR70 at each time point. The secondary endpoints are summarized descriptively. The secondary objectives were to assess the safety and immunogenicity of AMGEVITA compared with HUMIRA®.

Study Results

The ACR20 response rates at week 24 based on LOCF methodology were comparable between AMGEVITA and HUMIRA®. At week 24, 74.6% of subjects (194 of 260 subjects) in the AMGEVITA group and 72.4% of subjects (189 of 261) in the HUMIRA® group met the ACR20 response criteria. The 2 sided 90% CI risk ratio of ACR20 for AMGEVITA versus HUMIRA® was (0.954, 1.133) which fell within the pre-specified equivalence margin (0.738, 1/0.738). The 2 sided 95% CI of risk ratio of ACR20 for AMGEVITA versus HUMIRA® was (0.938, 1.152).

As a sensitivity analysis, the ACR20 response rate was analysed using non-responder imputation methodology (see [Table 20](#))

Table 20 Analysis of ACR20 at Week 24 (Full Analysis Set with Non-responder Imputation)

| Timepoint | AMGEVITA (N = 264) | HUMIRA® (N = 262) |
|--|-----------------------|----------------------|
| Week 24 | | |
| ACR20 Responder [n/N1 (%)] | 188/264 (71.2%) | 189/262 (72.1%) |
| 95% CI for the Response Rate (%) | (65.3, 76.6) | (66.3, 77.5) |
| ACR20 Non-Responder [n/N1 (%)] | 76/264 (28.8%) | 73/262 (27.9%) |
| Risk Ratio of ACR20 ^a | 1.000 | |
| 95% CI for Risk Ratio of ACR20 ^a | (0.899, 1.113) | |
| Risk Difference of ACR20 (%) ^a | 0.371 | |
| 95% CI for Risk Difference of ACR20 ^a | (-8.030, 7.289) | |

^a Based on a generalized linear model adjusted for geographic region and prior biologic use for rheumatoid arthritis as covariates in the model.

The pre-defined equivalence margin for risk ratio of ACR20 at week 24 between AMGEVITA and adalimumab is (0.738, 1/0.738) for RA study.

Definition(s): ACR20 = American College of Rheumatology Response Criteria; n = Number of subjects meeting the criteria at the visit; N1 = Number of subjects who were randomized and had an assessment at the visit.

Secondary efficacy endpoints were comparable between the biosimilar and the reference biologic drug.

Plaque Psoriasis

Study 20120263, a randomized, double-blind, active comparator-controlled study in adult subjects with moderate to severe plaque psoriasis, evaluated the efficacy of AMGEVITA compared with HUMIRA® as the primary objective.

The efficacy and safety of AMGEVITA were assessed in 350 patients ≥ 18 years of age with moderate to severe plaque psoriasis who were candidates for systemic therapy or phototherapy. Patients had stable moderate to severe plaque psoriasis for at least 6 months, a body surface area (BSA) ≥ 10%, and Psoriasis Area and Severity Index (PASI) ≥ 12 at study entry. The patients received AMGEVITA or HUMIRA® at an initial loading dose of 80 mg administered SC on week 1/day 1, followed by 40 mg subcutaneous (SC) given every other week starting one week after the loading dose. At week 16, subjects with a PASI 50 response or better continued on study for up to 52 weeks. Eligible subjects who continued treatment beyond week 16 were re-randomized in a blinded fashion such that all subjects initially randomized to AMGEVITA continued treatment with AMGEVITA, and subjects initially randomized to HUMIRA® either continued treatment with HUMIRA® or underwent a single transition to AMGEVITA in a 1:1 ratio.

The primary efficacy endpoint was PASI percent improvement from baseline at week 16. Secondary efficacy endpoints were analyzed to assess PASI percent improvement from baseline to weeks 32 and 50, PASI 75 response at weeks 16, 32, and 50; sPGA responses at weeks 16, 32, and 50, and percent of BSA involvement at weeks 16, 32, and 50.

The secondary objectives were to assess the safety and immunogenicity of AMGEVITA compared with HUMIRA®.

Study Results

At week 16, the PASI percent improvement from baseline was 80.91 in the AMGEVITA group and 83.06 in the HUMIRA® group. The per protocol analysis and additional sensitivity analysis (tipping point analysis) were supportive of the primary analysis. The least-squares (LS) mean difference of PASI percent improvement from baseline to week 16 between AMGEVITA and HUMIRA® was -2.18 with the 2-sided 95% CI of (-7.39, 3.02). The 95% CI was within the predefined equivalence margin. A tabular summary of the results is presented in [Table 21](#).

Table 21 Summary of PASI Percent Improvement from Baseline Through Week 16 (Full Analysis Set, LOCF)

| Time Point | AMGEVITA (N = 175) | | HUMIRA® (N = 175) | |
|------------------------------------|-----------------------|--|----------------------|--|
| | PASI Score | PASI % Improvement from Baseline | PASI Score | PASI % Improvement from Baseline |
| Baseline | | | | |
| n | 174 | | 173 | |
| Mean (SD) | 19.68 (8.100) | | 20.48 (7.880) | |
| Week 16 | | | | |
| n | 172 | 172 | 173 | 173 |
| Mean (SD) | 3.74 (5.094) | 80.91 (24.237) | 3.29 (5.795) | 83.06 (25.195) |
| Treatment difference ^a | | -2.18 | | |
| 95% CI for difference ^a | | (-7.39, 3.02) | | |

Pre-defined margin for testing similarity in PASI% improvement from baseline to week 16.

^a Estimated using ANCOVA model adjusted for the following factors: prior biologic use for psoriasis, region, and baseline PASI score.

The pre-defined equivalence margin for difference of PASI % improvement from baseline to week 16 between AMGEVITA and adalimumab is ±15 for psoriasis study.

Definition(s): ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; PASI = Psoriasis Area and Severity Index; SD = standard deviation

Secondary efficacy endpoints were comparable between the biosimilar and the reference biologic drug.

15.2.2.2 Safety

The types, frequency and severity of adverse events were comparable between the biosimilar and the reference biologic drug.

15.2.2.3 Immunogenicity

Patients with rheumatoid arthritis and psoriasis were treated with AMGEVITA or HUMIRA® and tested at multiple time points for anti-drug antibodies.

In the rheumatoid arthritis study, 264 and 262 subjects were administered AMGEVITA or HUMIRA®, respectively, for up to 22 weeks. Overall, 38.3% (101 of 264 subjects) in the AMGEVITA group and 38.2% (100 of 262 subjects) in the HUMIRA® group developed binding antibodies post-baseline ([Table 22](#)). During the course of the study, 9.1% and 11.1% of subjects developed neutralizing antibodies in the AMGEVITA and HUMIRA® groups, respectively.

Table 22 Rheumatoid Arthritis study

| Time Point | AMGEVITA Binding antibody [N= 264] (%) | Adalimumab (HUMIRA®) Binding antibody [N=262] (%) |
|-------------------|---|--|
| Baseline | 5 (1.9) | 6 (2.3) |
| Week 4 | 50 (18.9) | 45 (17.2) |
| Week 12 | 62 (23.5) | 62 (23.7) |
| Week 26 | 84 (31.8) | 92 (35.1) |
| Overall # | 101 (38.3) | 100 (38.2) |

Binding Antibody Positive Post-baseline with a Negative or No Result at Baseline

In the adult psoriasis study, 174 and 173 subjects were administered AMGEVITA or HUMIRA®, respectively, for up to 14 weeks. At week 16, the group that received HUMIRA® was re-randomized and 79 continued to receive HUMIRA®, while 77 subjects received AMGEVITA from week 16 through week 48. The incidences of binding antibody positive patients at week 16 were 48.9% and 57.2% (Table 23). In patients administered AMGEVITA or HUMIRA® for up to 48 weeks, the percentages of subjects testing positive for binding antibodies at 52 weeks were 42.8% and 43.0% (Table 24), respectively.

During the course of the study, 68.4% and 74.7% of subjects, receiving AMGEVITA or HUMIRA®, developed binding antibodies, respectively. Neutralizing antibodies were detected in 13.8% and 20.3% of subjects receiving, AMGEVITA or HUMIRA®, respectively, by Week 52.

Table 23 Psoriasis Study (Through Week 16)

| Time Point | AMGEVITA Binding antibody [N = 174] (%) | Adalimumab (HUMIRA®) Binding antibody [N = 173] (%) |
|-------------------|--|--|
| Baseline | 1 (0.6) | 2 (1.2) |
| Week 4 | 50 (28.7) | 48 (27.7) |
| Week 16 | 85 (48.9) | 99 (57.2) |

Table 24 Psoriasis Study (Week 16 through 52)

| Time Point | AMGEVITA Binding antibody [N = 152] (%) | Adalimumab (HUMIRA®) Binding antibody [N = 79] (%) | Adalimumab (HUMIRA®)/AMGEVITA Binding antibody [N = 77] (%) |
|-------------------|--|---|--|
| Week 16 | 72 (47.4) | 43 (54.4) | 48 (62.3)* |
| Week 20 | 83 (54.6) | 47 (59.5) | 50 (64.9) |
| Week 32 | 76 (50.0) | 45 (57.0) | 46 (59.7) |
| Week 52 | 65 (42.8) | 34 (43.0) | 42 (54.5) |
| Overall # | 104 (68.4) | 59 (74.7) | 56 (72.7) |

* Rates indicated are prior to receiving AMGEVITA, subjects received only HUMIRA® up to week 16

Binding Antibody Positive Post-baseline with a Negative or No Result at Baseline

The incidences presented are based on the combined results from both AMGEVITA and HUMIRA® ADA assays and reflect the percentage of patients whose test results were considered positive for antibodies to either AMGEVITA or HUMIRA®.

16 COMPARATIVE NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY

16.1 Comparative Non-Clinical Pharmacodynamics

This section summarizes the extensive comparative studies that were conducted to compare the pharmacology of AMGEVITA to HUMIRA®.

The binding to TNF α and to Fc receptors (FcRs), potency of inhibition of TNF α -induced activities, and effector function activities of AMGEVITA have been assessed in comparative *in vitro* studies with HUMIRA® (adalimumab, US and EU) and were found to be similar. These assays probed multiple aspects of TNF α signaling including inhibition of pro-inflammatory chemokine induction and cell death. In addition, inhibitory activity has been demonstrated both in cell lines and in 50% whole blood. In order to compare activities which are mediated by mbTNF α , similarity in the ability to inhibit cellular proliferation in an MLR was also demonstrated.

Measures of Fc-mediated activities including binding to Fc γ R1a, Fc γ R11a, and Fc γ R111a (158F) were also compared and found to be similar between AMGEVITA and adalimumab (US and EU). Adalimumab is known to form complexes when bound to sTNF α , which can affect Fc γ R111a binding. Similarity between AMGEVITA and adalimumab (US and EU) in Fc γ R111a (158V) binding was also demonstrated in the presence of sTNF α . The specificity of AMGEVITA was confirmed by demonstrating a lack of inhibitory activity against LT α , the most highly related cytokine to TNF α .

Safety and pharmacokinetic studies have been conducted in cynomolgus monkeys, and the panel of pharmacology assays has demonstrated high affinity binding and neutralization of cynomolgus monkey TNF α . Therefore, these results together with the monkey toxicology study results support that AMGEVITA and adalimumab are similar from the functional and toxicological perspectives and likely to have similar efficacy and safety profile.

Table 25 Functional Similarity Assessment Comparing AMGEVITA with Adalimumab

| Method | Relevant Activity |
|---|----------------------|
| Primary characterization assays | |
| Apoptosis inhibition bioassay (Potency) | TNF α |
| sTNF α binding | TNF α |
| Fc γ RIIIa (158V) Binding | FcR |
| ADCC | FcR and TNF α |
| CDC | FcR and C1q |
| Binding to FcRn | FcR |
| Additional characterization assays | |
| On and off rates (human TNF α) | TNF α |
| On and off rates (cynomolgus TNF α) | TNF α |
| mbTNF Binding | TNF α |
| Inhibition of sTNF α -induced IL-8 in HUVEC | TNF α |
| Specificity against LT α in the HUVEC assay | TNF α |
| Inhibition of human sTNF α - induced cell death in L929 cells | TNF α |
| Inhibition of cynomolgus sTNF α - induced cell death in L929 cells | TNF α |
| Inhibition of sTNF α -induced chemokines in human whole blood | TNF α |
| Inhibition of sTNF α -induced chemokines in cynomolgus whole blood | TNF α |
| Inhibition of proliferation in a mixed lymphocyte reaction | FcR and TNF α |
| Fc γ R1a Binding | FcR |
| Fc γ RIIa (131H) Binding | FcR |
| Fc γ RIIIa (158F) Binding | FcR |
| Fc γ RIIIa (158V) + TNF α Binding | FcR |

Definition(s): ADCC = antibody-dependent cell-mediated cytotoxicity; C1q = first subcomponent of the C1 complex of the classical pathway of complement activation; CDC = complement-dependent cytotoxicity; Fc = fragment crystallizable; FcR = Fc receptor; FcRn = neonatal Fc receptor; Fc γ R1a = Fc gamma receptor Type Ia; Fc γ RIIa = Fc gamma receptor Type IIa; Fc γ RIIIa = Fc gamma receptor Type IIIa; H = Histidine; V = Valine; F = phenylalanine; HUVEC = human umbilical vein endothelial cells; L929 = mouse fibroblast cells; TNF α = tumour necrosis factor alpha; LT α = lymphotoxin alpha; IL-8 = interleukin 8.

16.2 Comparative Toxicology

This section summarizes the comparative toxicity studies that were conducted to compare AMGEVITA to HUMIRA®.

A non-terminal study in male cynomolgus monkeys and a 1-month terminal repeat-dose study in male and female monkeys (Table 26) were conducted to evaluate whether the nonclinical safety for AMGEVITA and HUMIRA® are similar with no meaningful differences between the two products.

Table 26 Overview of the Toxicology Program

| Study Type | Sex and Species | Dosing Regimen | Test Article | GLP | Study Number |
|--|-----------------------------------|--------------------|--------------------------|-----|--------------|
| 2-week nonterminal comparative repeat-dose | Male cynomolgus monkey | 32 mg/kg SC QW | AMGEVITA HUMIRA® (US) | Yes | 114832 |
| 1-month comparative repeat-dose | Male and female cynomolgus monkey | 0, 157 mg/kg SC QW | AMGEVITA HUMIRA® (US) | Yes | 115674 |

Definition(s): GLP = Good Laboratory Practice; QW = once weekly; SC = subcutaneous; US = United States

In the nonterminal comparative study in male cynomolgus monkey (Study 114832), AMGEVITA and HUMIRA® at 32 mg/kg were well tolerated. Toxicokinetic parameters for both groups after the first dose are shown in [Table 27](#). Consistent with data available for historical nonclinical studies with adalimumab, there were no effects on clinical signs, body weights, hematology, serum chemistry, or coagulation parameters.

Table 27 Toxicokinetic Parameters in Cynomolgus Monkeys After Subcutaneous Once Weekly Administration of AMGEVITA or HUMIRA®

| Study Number and Study Type | Sex and Species | Dose Regimen and Test Article | C _{max} (µg/mL) | | AUC _{last} (µg•hr/mL) | |
|--|--|-------------------------------|--------------------------|--------|--------------------------------|---------|
| | | | Day 1 | Day 22 | Day 1 | Day 22 |
| 114832 2-week nonterminal comparative repeat-dose | Male cynomolgus monkey | 32 mg/kg SC QW AMGEVITA | 244 | -- | 34,100 | -- |
| | | 32 mg/kg SC QW HUMIRA® | 280 | -- | 38,300 | -- |
| 115674 1-month comparative repeat-dose | Male and female ^a cynomolgus monkey | 157 mg/kg SC QW AMGEVITA | 1,030 | 2,660 | 145,000 | 380,000 |
| | | 157 mg/kg SC QW HUMIRA® | 1,130 | 2,640 | 154,000 | 380,000 |

-- = not applicable; there was no day 22 timepoint;

^a Data for males and females were combined because no gender differences were observed

Definition(s): AUC_{last} = area under the concentration-time curve from time 0 to the last measured time point; C_{max} = maximum observed concentration; QW = once weekly; SC = subcutaneous.

The second comparative toxicology study was conducted at a higher dose in both sexes and included a vehicle control and special endpoints to assess effects on tissue lymphoid cells (Study 115674). Toxicokinetic parameters for AMGEVITA and HUMIRA® are shown in [Table 27](#). Toxicokinetic profiles were comparable between AMGEVITA and HUMIRA® with no sex differences ([Table 27](#)). There was a moderate accumulation in exposure after the fourth dose of AMGEVITA and HUMIRA®. No antidrug antibodies were detected in the AMGEVITA or HUMIRA® groups. There were no effects on clinical signs, body weight, food consumption, physiologic measurements, ophthalmic or electrocardiogram examinations, serum chemistry, urinalysis, or on macroscopic necropsy observations. A transient increase in neutrophil count and fibrinogen concentration was observed on day 4 in some animals administered AMGEVITA or HUMIRA®; levels were normal on day 29. Consistent with historical microscopic findings after adalimumab treatment, the histological changes for AMGEVITA and HUMIRA® were limited to lymphoid tissues. Changes were similar for AMGEVITA and HUMIRA® and included mild to

moderate decreased size and number of germinal centers in axillary lymph node, mesenteric lymph node, and tonsil. In the spleen, decreased CD21+ B lymphocytes were observed by immunohistochemical staining and by flow cytometry; the decreases were similar for AMGEVITA and HUMIRA®.

17 CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG

17.1 Adult

17.1.1 Rheumatoid Arthritis

Study Demographics and Trial Design

The efficacy and safety of adalimumab were assessed in five randomized, double-blind studies in patients ≥ 18 years of age with active rheumatoid arthritis diagnosed according to the ACR criteria. Patients had at least six swollen and nine tender joints. adalimumab was administered subcutaneously in combination with MTX (12.5 to 25 mg, Studies DE009, DE019 and DE013), or as monotherapy (Studies DE011 and DE013), or with other disease-modifying anti-rheumatic drugs (DMARDs) (Study DE031). [Table 28](#) summarizes the controlled clinical trials that were done in patients with active rheumatoid arthritis.

Table 28 Summary of Controlled Clinical Trials Supporting Safety and Efficacy in Patients with Rheumatoid Arthritis

| Study # | Trial Design | Dosage, Route of Administration and Duration | Study Subjects (n) | Mean Age (Range) | Gender (% Female) |
|----------------|---|--|--------------------|------------------|-------------------|
| DE009 (RA I) | Multicenter, double-blind, randomized, placebo-controlled | Adalimumab 20 mg, 40 mg, or 80 mg; eow | 200 | 54.8 ± 11.9 | 75.5 |
| | | Placebo Subcutaneous 24 weeks | 60 | 55.2 ± 10.9 | 83.3 |
| DE011 (RA II) | Multicenter, double-blind, randomized, placebo-controlled | Adalimumab 20 mg or 40 mg; ew or eow | 434 | 53.0 ± 12.3 | 77.4 |
| | | Placebo Subcutaneous 26 weeks | 110 | 53.5 ± 13.2 | 77.3 |
| DE019 (RA III) | Multicenter, double-blind, randomized, placebo-controlled | Adalimumab 20 mg ew or 40 mg eow | 419 | 56.2 ± 12.1 | 75.9 |
| | | Placebo Subcutaneous 52 weeks | 200 | 55.6 ± 12.0 | 73.0 |
| | Open-label extension | Adalimumab 40 mg eow up to 10 years | 457 | 55.7 ± 12.02 | 74.7 |

| Study # | Trial Design | Dosage, Route of Administration and Duration | Study Subjects (n) | Mean Age (Range) | Gender (% Female) |
|-------------------------------------|--|--|--------------------|------------------|-------------------|
| DE031 (RA IV) | Multicenter, double-blind, randomized, placebo-controlled | Adalimumab 40 mg eow | 315 | 55.2 ± 12.7 | 80.0 |
| | | Placebo Subcutaneous 24 weeks | 315 | 55.7 ± 12.4 | 79.7 |
| DE009, DE011, DE019, DE031 Combined | Multicenter, double-blind, randomized, placebo-controlled | Adalimumab | 1368 | 54.7 ± 12.3 | 77.3 |
| | | Placebo | 685 | 55.3 ± 12.3 | 77.7 |
| DE013 (RA V) | Phase 3, multicenter, double-blind, active comparator-controlled, parallel-group | Adalimumab 40 mg eow | 274 | 52.1 ± 13.5 | 77.4 |
| | | Adalimumab 40 mg eow + MTX ew | 268 | 51.9 ± 14.0 | 72.0 |
| | | MTX ew | 257 | 52.0 ± 13.1 | 73.9 |
| | | Subcutaneous and oral 104 weeks | | | |

Definition(s): ew = every week; eow = every other week; MTX = methotrexate

Mean ages across the four studies ranged from 53.0 years (adalimumab group, Study DE011) to 56.2 years (adalimumab group, Study DE019). The mean age in Study DE013 was 51.9 years (adalimumab + MTX group) to 52.0 years (MTX group). Mean weight ranged from 68.5 kg (adalimumab group, Study DE011) to 80.3 kg (placebo group, Study DE019). The mean weight in Study DE013 was 74.4 kg (adalimumab group) to 76.8 kg (adalimumab + MTX group). As expected, based on the demographics of the disease, patients were predominantly female, with the percentage of female patients ranging from 73.0% (placebo group, Study DE019) to 83.3% (placebo group, Study DE009). Similarly, the percentage of females in Study DE013 ranged from 72.0% (adalimumab + MTX group) to 77.4% (adalimumab group). Patients were predominantly Caucasian, with the percentage of Caucasian patients ranging from 75.0% (placebo group, Study DE009) to 99.1% (placebo group, Study DE011). The percentage of Caucasian patients in Study DE013 ranged from 93.3% (adalimumab + MTX group) to 94.2% (MTX group). The high percentage of Caucasian patients in Study DE011 was consistent with the populations of the geographic regions in which this study was conducted (ie, Europe, Canada, and Australia). Overall, the demographic characteristics of the study patients were fairly representative of rheumatoid arthritis in the general population. There were no notable differences between the studies in any of the demographic characteristics analyzed.

Description of Clinical Studies

Adalimumab was evaluated in over 3,000 patients in all rheumatoid arthritis clinical trials. Some patients were treated for up to 10 years. The efficacy and safety of adalimumab were assessed in five randomized, double-blind, well-controlled studies.

Study DE009 evaluated 271 patients with moderately to severely active rheumatoid arthritis who had failed therapy with at least one but no more than four DMARDs, and had inadequate response to MTX.

Study DE011 evaluated 544 patients with moderately to severely active rheumatoid arthritis who had failed therapy with at least one DMARD. Doses of placebo, 20 or 40 mg of adalimumab were given by subcutaneous injection as monotherapy every other week or weekly for 26 weeks.

Study DE019 evaluated 619 patients with moderately to severely active rheumatoid arthritis who had an inadequate response to MTX. Patients received placebo, 40 mg of adalimumab every other week with placebo injections on alternate weeks, or 20 mg of adalimumab weekly for up to Week 52. Study DE019 had an additional primary endpoint at Week 52 of inhibition of disease progression (as detected by X-ray results). Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of adalimumab was administered every other week for up to ten years. 202 patients completed 10 years of the study; the efficacy demonstrated at 5 years (reduction in signs and symptoms of rheumatoid arthritis, improvement in physical function, inhibition of structural joint damage, and rates of clinical response including remission) was maintained through 10 years with continued adalimumab in these patients. For efficacy results in these patients, (see **CLINICAL TRIALS, Adult, Rheumatoid Arthritis [17.1.1], Study Results, Clinical Response, Studies DE009, DE011 and DE019; Radiographic Response; and Quality of Life and Physical Function Response**). For a description of safety in these patients, (see **Adverse Drug Reaction Overview [9.1]**).

Study DE031 assessed safety in 636 patients with moderately to severely active rheumatoid arthritis who were either DMARD-naïve or were permitted to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. Patients were randomized to 40 mg of adalimumab or placebo every other week for 24 weeks.

Study DE013 evaluated 799 patients with moderate to severely active early rheumatoid arthritis (disease duration less than three years) who were ≥ 18 years old and MTX naïve. This study compared the efficacy of adalimumab + MTX combination therapy and MTX monotherapy in reducing the signs and symptoms and rate of progression of joint damage in rheumatoid arthritis. Patients were randomized to receive adalimumab 40 mg every other week + MTX combination therapy, adalimumab 40 mg every other week monotherapy, or MTX given weekly, for 104 weeks.

Study Results

Clinical Response

Studies DE009, DE011 and DE019

The percent of adalimumab-treated patients achieving ACR 20/50/70 responses was consistent across all three trials. The results of the three trials are summarized in [Table 29](#).

Table 29 ACR Responses in Placebo-Controlled Trials (Percent of Patients)

| Response | | Study DE009* | | Study DE011* | | | Study DE019* | |
|----------|-----------|-------------------------|--------------------------------------|--------------------|---------------------------------|--------------------------------|--------------------------|---------------------------------------|
| | | Placebo + MTX N = 60 | Adalimumab 40 mg eow + MTX N = 63 | Placebo N = 110 | Adalimumab 40 mg eow N = 113 | Adalimumab 40 mg ew N = 103 | Placebo + MTX N = 200 | Adalimumab 40 mg eow + MTX N = 207 |
| ACR 20 | 6 months | 13.3% | 65.1%** | 19.1% | 46.0%** | 53.4%** | 29.5% | 63.3%** |
| | 12 months | NA | NA | NA | NA | NA | 24.0% | 58.9%** |
| ACR 50 | 6 months | 6.7% | 52.4%** | 8.2% | 22.1%** | 35.0%** | 9.5% | 39.1%** |
| | 12 months | NA | NA | NA | NA | NA | 9.5% | 41.5%** |
| ACR 70 | 6 months | 3.3% | 23.8%** | 1.8% | 12.4%** | 18.4%** | 2.5% | 20.8%** |
| | 12 months | NA | NA | NA | NA | NA | 4.5% | 23.2%** |

* Study DE009 at Week 24, Study DE011 at Week 26, and Study DE019 at Weeks 24 and 52** p < 0.01 for adalimumab versus placebo

Definition(s): MTX = methotrexate; ACR = American College of Rheumatology; eow = every other week; ew = every week

The results of the components of the ACR response criteria for Studies DE011 and DE019 are shown in [Table 30](#). ACR response rates and improvement in all components of ACR response were maintained to Week 104. Over the two years in Study DE019, 24% of adalimumab patients receiving 40 mg every other week achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period. ACR responses were maintained in similar proportions of patients for up to five years with continuous adalimumab treatment in the open-label portion of Study DE019.

Table 30 Components of ACR Response in Studies DE011 and DE019

| Parameter (median) | Study DE011 | | | | Study DE019 | | | | | |
|--|--------------------|---------|------------------------------------|---------|--------------------------|---------|---------|---------------------------------------|---------|---------|
| | Placebo N = 110 | | Adalimumab 40 mg eow N = 103 | | Placebo + MTX N = 200 | | | Adalimumab 40 mg eow + MTX N = 207 | | |
| | Baseline | Week 26 | Baseline | Week 26 | Baseline | Week 24 | Week 52 | Baseline | Week 24 | Week 52 |
| Number of tender joints (Scale 0 to 68) | 35 | 26 | 31 | 16** | 26 | 15 | 15 | 24 | 8.0* | 6.0* |
| Number of swollen joints (Scale 0 to 66) | 19 | 16 | 18 | 10** | 17 | 11 | 11 | 18 | 5.0* | 4.0* |
| Physician global assessment disease activity [†] | 7 | 6.1 | 6.6 | 3.7** | 6.3 | 3.5 | 3.8 | 6.5 | 2.0* | 1.6* |
| Patient global assessments disease activity [†] | 7.5 | 6.3 | 7.5 | 4.5** | 5.4 | 3.9 | 4.3 | 5.2 | 2.0* | 1.8* |
| Pain [†] | 7.3 | 6.1 | 7.3 | 4.1** | 6 | 3.8 | 4.6 | 5.8 | 2.1* | 1.9* |
| Disability index (HAQ) [‡] | 2 | 1.9 | 1.9 | 1.5** | 1.5 | 1.25 | 1.25 | 1.5 | 0.75* | 0.75* |
| CRP (mg/dL) | 3.9 | 4.3 | 4.6 | 1.8** | 1 | 0.9 | 0.9 | 1 | 0.40* | 0.40* |

[†] Visual analogue scale; 0 = best; 10 = worst

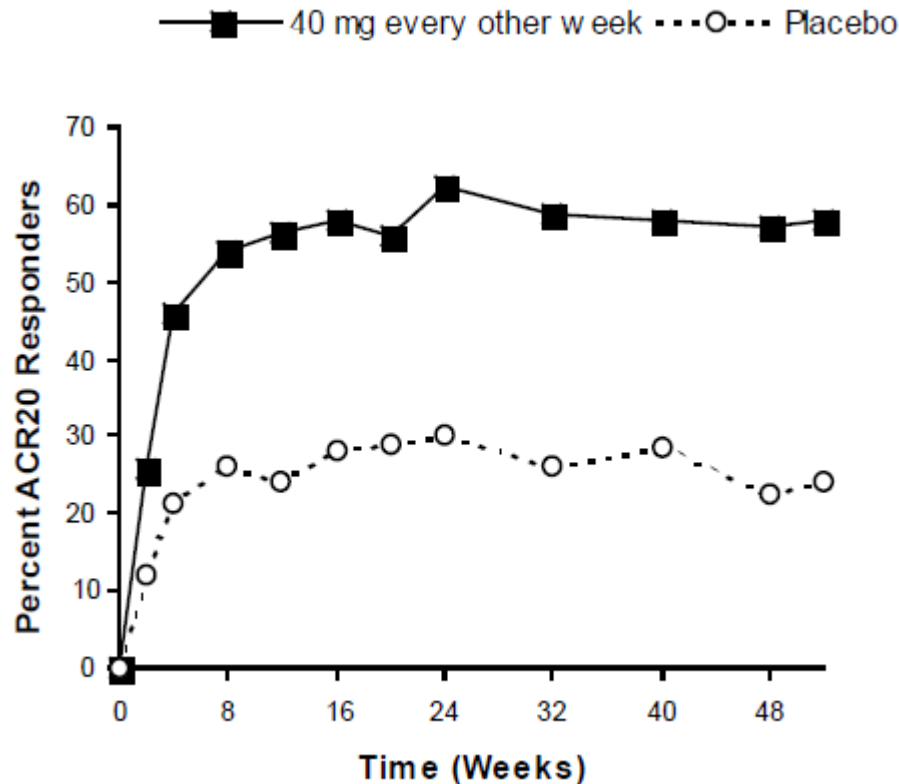
[‡] Disability index of the Health Assessment Questionnaire (HAQ); 0 = best; 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity

* p < 0.001 for adalimumab versus placebo, based on mean change from baseline

Definition(s): ACR = American College of Rheumatology; MTX = methotrexate; CRP = C-reactive protein; eow = every other week

The time course of ACR 20 response for Study DE019 is shown in Figure 2. In Study DE019, 85% of patients with ACR 20 responses at Week 24 maintained the response at Week 52. The time course of ACR 20 response for Studies DE009 and DE011 were similar.

Figure 2 Study DE019 ACR 20 Responses Over 52 Weeks



In the open-label extension for Study DE019, durable and sustained ACR 20, 50 and 70 responses have been observed through 5 and 10 years. Of 207 patients, 114 patients continued on adalimumab 40 mg every other week for 5 years. Among those, 86 patients (75.4%) had ACR 20 responses; 72 patients (63.2%) had ACR 50 responses; and 41 patients (36%) had ACR 70 responses. Of 207 patients, 81 patients continued on adalimumab 40 mg every other week for 10 years. Among those, 64 patients (79.0%) had ACR 20 responses; 56 patients (69.1%) had ACR 50 responses; and 43 patients (53.1%) had ACR 70 responses.

Study DE031

In Study DE031, 53% of patients treated with adalimumab 40 mg every other week plus standard of care had an ACR 20 response at Week 24 compared to 35% on placebo plus standard of care ($p < 0.001$). No unique adverse reactions related to the combination of adalimumab and other DMARDs were observed.

In all four studies, adalimumab-treated patients achieved ACR 20/50/70 responses faster and more often than placebo-treated patients. In Study DE009, there was a statistically significant difference in ACR 20 responses at Week 1 (first study visit) between patients treated with adalimumab (26.0%) and placebo (5.0%). Statistically significant differences in ACR 20 responses were also seen in Studies DE011, DE019 and DE031 at Week 2 (first study visit) between patients treated with adalimumab (36.4, 29.1 and 33.7%, respectively) and placebo

(7.3, 13.0 and 8.6%, respectively). A similar pattern of the time to first ACR 50 and 70 responses was noted in all four studies.

Study DE013

In Study DE013, for early rheumatoid arthritis patients who were MTX naïve, the combination therapy with adalimumab + MTX led to faster and significantly greater ACR responses than MTX monotherapy at Week 52, and responses were sustained at Week 104. The clinical responses for Study DE013 are presented in [Table 31](#).

At Week 52, all individual components of the ACR response criteria improved with adalimumab + MTX therapy, and improvements were maintained to Week 104.

Over the two-year study, 48.5% of patients who received adalimumab + MTX combination therapy achieved a major clinical response (ACR 70 for six continuous months) compared to 27.2% of patients who received MTX monotherapy ($p < 0.001$).

Table 31 Clinical Responses in Study DE013 (All Randomized Subjects)

| Response | | MTX ^a N = 257 (%) | Adalimumab ^b N = 274 (%) | Adalimumab + MTX N = 268 (%) |
|--------------------------------------|----------|------------------------------------|---|------------------------------------|
| ACR 20 | Week 52 | 62.6 | 54.4 | 72.8 |
| | Week 104 | 56.0 | 49.3 | 69.4 |
| ACR 50 | Week 52 | 45.9 | 41.2 | 61.6 |
| | Week 104 | 42.8 | 36.9 | 59.0 |
| ACR 70 | Week 52 | 27.2 | 25.9 | 45.5 |
| | Week 104 | 28.4 | 28.1 | 46.6 |
| Major Clinical Response ^c | | 27.2 | 24.5 | 48.5 |

^a $p < 0.05$ for adalimumab + MTX versus MTX for ACR 20

$p < 0.001$ for adalimumab + MTX versus MTX for ACR 50 and 70 and Major Clinical Response

^b $p < 0.001$ for adalimumab + MTX versus adalimumab

^c Major Clinical Response is achieving ACR 70 response for a continuous six-month period

Definition(s): MTX = methotrexate; ACR = American College of Rheumatology

At Week 52 and Week 104 of treatment in Study DE013, adalimumab + MTX combination therapy was superior to MTX monotherapy in achieving a low disease state in patients with recently diagnosed moderate to severe rheumatoid arthritis, as demonstrated by the number of patients who achieved clinical remission [disease activity score (DAS28) < 2.6] at Week 52 and change from baseline in DAS28 at Week 52 and Week 104.

DAS28 responses for Study DE013 are presented in [Table 32](#)

Table 32 Change in DAS28 from Baseline at Weeks 52 and 104 in Study DE013 (All Randomized Subjects)

| DAS28 | | MTX N = 257 | Adalimumab N = 274 | Adalimumab + MTX N = 268 |
|----------|---|-------------------------|-------------------------|-----------------------------|
| Week 52 | n | 184 | 185 | 206 |
| | Baseline (mean) | 6.3 | 6.4 | 6.3 |
| | Change at Week 52 (mean ± SD) | -2.8 ± 1.4 ^a | -2.8 ± 1.5 ^b | -3.6 ± 1.3 |
| | % of subjects in remission (DAS28 < 2.6) at Week 52 | 20.6% ^a | 23.4% ^b | 42.9% |
| Week 104 | n | 161 | 158 | 191 |
| | Baseline (mean) | 6.3 | 6.3 | 6.3 |
| | Change at Week 104 (mean ± SD) | -3.1 ± 1.4 ^a | -3.2 ± 1.4 ^b | -3.8 ± 1.3 |
| | % of subjects in remission (DAS28 < 2.6) at Week 104 | 24.9% | 25.2% | 49.3% |

^a p < 0.001 for adalimumab + MTX versus MTX

^b p < 0.001 for adalimumab + MTX versus adalimumab

Definition(s): MTX = methotrexate; DAS = disease activity score; SD = standard deviation

Radiographic Response

In Study DE019, where adalimumab-treated patients had a mean duration of rheumatoid arthritis of approximately 11 years, structural joint damage was assessed radiographically and expressed as change in total Sharp score (TSS) and its components, the erosion score and joint space narrowing (JSN) score at Month 12 compared to baseline. At baseline, the median TSS was approximately 55 in the placebo and 40 mg every other week groups. The 12-month results are shown in [Table 33](#). Adalimumab + MTX-treated patients demonstrated less radiographic progression than patients receiving MTX alone at Week 52.

Table 33 Radiographic Mean Changes Over 12 Months in Study DE019 with Background Methotrexate

| LOCF | Placebo + MTX N = 200 | Adalimumab ^a + MTX N = 207 | Adalimumab ^a + MTX and Placebo + MTX (95% CI ^{**}) | p-value |
|---|--------------------------|--|---|----------|
| Change in Modified Total Sharp Score (Mean) | 2.7 | 0.1 | -2.6 (1.4, 3.8) | < 0.001* |
| Change in Erosions (Mean) | 1.6 | 0 | -1.6 (0.9, 2.2) | < 0.001 |
| Change in JSN Score (Mean) | 1 | 0.1 | -0.9 (0.3, 1.4) | 0.002 |

^a 40 mg administered every other week

* Based on analysis of ranked ANCOVA

** 95% confidence intervals for the differences in change scores between MTX and adalimumab

Definition(s): MTX = methotrexate; LOCF = last observation carried forward; JSN = joint space narrowing; CI = confidence interval

Data from the open-label extension of Study DE019 indicate that the reduction in rate of progression of structural damage is maintained for 8 and 10 years in a subset of patients. At 8 years, 81 of 207 patients originally treated with 40 mg adalimumab every other week were evaluated radiographically. Among those, 59.3% (48 patients) showed no progression of structural damage defined by a change from baseline in the mTSS of 0.5 or less. At 10 years, 79 of 207 patients originally treated with 40 mg adalimumab every other week were evaluated radiographically. Among those, 50.6% (40 patients) showed no progression of structural damage defined by a change from baseline in the mTSS of 0.5 or less.

In Study DE013, adalimumab-treated patients had a mean duration of rheumatoid arthritis of less than nine months and had not previously received MTX. Structural joint damage was assessed radiographically and expressed as change in modified total Sharp score (TSS). The Week 52 results are shown in Table 34. A statistically significant difference for change in modified total Sharp score, erosion score and JSN were observed at Week 52 and maintained at Week 104.

Table 34 Radiographic Mean Change (95% Confidence Interval) in Study DE013

| | Response | MTX^a N = 257 | Adalimumab^{a,b} N = 274 | Adalimumab + MTX N = 268 |
|----------|-------------------|------------------------------------|---|---|
| Week 52 | Total Sharp Score | 5.7 (4.2, 7.3) | 3.0 (1.7, 4.3) | 1.3 (0.5, 2.1) |
| | Erosion Score | 3.7 (2.7, 4.8) | 1.7 (1.0, 2.4) | 0.8 (0.4, 1.2) |
| | JSN Score | 2.0 (1.2, 2.8) | 1.3 (0.5, 2.1) | 0.5 (0.0, 1.0) |
| Week 104 | Total Sharp Score | 10.4 (7.7, 13.2) | 5.5 (3.6, 7.4) | 1.9 (0.9, 2.9) |
| | Erosion Score | 6.4 (4.6, 8.2) | 3.0 (2.0, 4.0) | 1.0 (0.4, 1.6) |
| | JSN Score | 4.1 (2.7, 5.4) | 2.6 (1.5, 3.7) | 0.9 (0.3, 1.5) |

^a p < 0.001 for adalimumab + MTX versus MTX at Week 52 and Week 104 and for adalimumab + MTX versus adalimumab at Week 104

^b p < 0.01 for adalimumab + MTX versus adalimumab at Week 52

Definition(s): MTX = methotrexate; JSN = joint space narrowing

The percentage of patients without progression (change from baseline in modified total Sharp score ≤ 0.5) was significantly higher with adalimumab + MTX combination therapy compared to MTX monotherapy at Week 52 (63.8 and 37.4% respectively, p < 0.001) and Week 104 (61.2 and 33.5% respectively, p < 0.001).

Quality of Life and Physical Function Response

In Studies DE009, DE011, DE019 and DE031, adalimumab showed significantly greater improvement than placebo in the disability index of Health Assessment Questionnaire (HAQ) from baseline to the end of study, and significantly greater improvement than placebo in the health outcomes as assessed by the Short Form Health Survey (SF-36). Improvement was seen in both the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

In Study DE019, the mean (CI) improvement in HAQ from baseline at Week 52 was -0.60 (-0.65, -0.55) for the adalimumab patients and -0.25 (-0.33, -0.17) for placebo + MTX (p < 0.001) patients. Eighty-two percent (82%) of adalimumab-treated patients who achieved a 0.5 or greater improvement in HAQ at Week 52 in the double-blind portion of the study

maintained that improvement through Week 104 of open-label treatment, and a similar proportion of patients maintained this response through Week 260 (five years) and Week 520 (10 years). After five years, the proportion of subjects who were HAQ responders at the 0.22, 0.50, 0.75 and 1.0 levels were 76.5, 60.0, 47.5 and 30.8% respectively. A total of 149 patients who received adalimumab for 10 years were assessed for HAQ. After 10 years, the proportions of patients who were HAQ responders at the 0.22, 0.50, 0.75 and 1.0 levels were 73.8 (n = 110), 57.0 (n = 85), 44.3 (n = 66) and 26.2% (n = 39) respectively. Improvement in SF-36 was measured and maintained up to Week 156 (3 years).

In Study DE013, the active comparator-controlled study in early rheumatoid arthritis, the improvement in the HAQ disability index, and the physical component of the SF-36, showed greater improvement ($p < 0.001$) for the adalimumab + MTX combination therapy versus the MTX monotherapy at Week 52, which was maintained through Week 104.

At Week 52 and Week 104 of treatment, 69.4% (186/268) and 63.8% (171/268) of subjects, respectively, treated with adalimumab + MTX combination therapy had a decrease (i.e., improvement) in the disability index of the HAQ of ≥ 0.3 units. In comparison, 61.5% (158/257; $p = 0.562$) and 53.3% (137/257; $p = 0.0146$) of subjects treated with MTX monotherapy, and 55.1% (151/274; $p < 0.001$) and 48.2% (132/274; $p < 0.001$) of subjects treated with adalimumab monotherapy had a decrease in the disability index of the HAQ of ≥ 0.3 units at Weeks 52 and 104, respectively.

17.1.2 Psoriatic Arthritis

The efficacy of adalimumab was assessed in two randomized, double-blind, placebo-controlled studies in 413 patients. The primary study treated 313 adult patients with moderately to severely active psoriatic arthritis who had an inadequate response to nonsteroidal anti-inflammatory drug (NSAID) therapy. Of the 313 treated in this study, 158 (50.5%) were described as taking MTX at the time of randomization. Doses of adalimumab 40 mg every other week were administered for 24 weeks. [Table 35](#) summarizes the controlled clinical trials that were done in patients with active psoriatic arthritis.

Table 35 Summary of Controlled Clinical Trials Supporting Safety and Efficacy in Patients with Psoriatic Arthritis

| Study # | Trial Design | Dosage, Route of Administration and Duration | Study Subjects (n) | Mean Age (Range) | Gender (% Female) |
|---------------------|---|---|--------------------|------------------------------------|-------------------|
| M02-518 (PsA I) | Multicenter, double-blind, randomized, placebo-controlled, stratified by MTX use and extent of psoriasis ($\geq 3\%$ or $< 3\%$ BSA) | Adalimumab 40 mg eow Placebo Subcutaneous 24 weeks | 151 162 | 48.6 \pm 12.5 49.2 \pm 11.1 | 43.7 45.1 |
| M02-570 (PsA II) | Multicenter, double-blind, randomized, placebo-controlled, stratified by DMARD use (yes, no) | Adalimumab 40 mg eow Placebo Subcutaneous 24 weeks | 51 49 | 50.4 \pm 11. 47.7 \pm 11.3 | 43.1 49.0 |
| M02-518 and M02-570 | Multicenter, double-blind, randomized, placebo-controlled, stratified with MTX (M02-518), and DMARDs (M02-570) | Adalimumab 40 mg eow Placebo Subcutaneous 24 weeks | 202 211 | 49.1 \pm 12.2 48.9 \pm 11.2 | 43.6 46.0 |

Definition(s): eow = every other week; MTX = methotrexate; BSA = body surface area; DMARDs = disease-modifying anti-rheumatic drugs

Mean ages across the two studies ranged from 47.7 years (placebo group, Study M02-570) to 50.4 years (adalimumab group, Study M02-570). Mean weight ranged from 85.5 kg (placebo group, Study M02-518) and 91.5 kg (adalimumab group, Study M02-570). The percentage of females ranged from 43.1 % (adalimumab group, Study M02-570) and 45.1% (placebo group, Study M02-518). Patients were predominantly Caucasian, with the percentage of Caucasian patients ranging from 93.8% (placebo group, Study M02-518) to 98.0% (adalimumab group, Study M02-570). There were no notable differences between the studies in any of the demographic characteristics analyzed. Upon completion of both studies, 383 patients enrolled in an open-label extension study (Table 36) in which adalimumab 40 mg is administered every other week.

Table 36 Summary of Open-Label Clinical Trials Evaluating Long-Term Safety and Efficacy in Patients with Psoriatic Arthritis

| Study # | Trial Design | Dosage, Route of Administration and Duration | Study Subjects (n) | Mean Age (Range) (Years) | Gender (% Female) |
|-------------------|--|--|--------------------|-----------------------------------|-------------------|
| M02-537 (PsA III) | Multicenter, open-label, multi-national continuation of studies M02-518 and M02-570. | Adalimumab 40 mg eow Subcutaneous 120 weeks or when commercially available, whichever is later | 395 | 49.0 \pm 11.7 (20.0 to 88.0) | 44.6 |

Definition(s): eow = every other week

Description of Clinical Studies

Study M02-518 evaluated the effectiveness and safety of adalimumab either alone or in combination with concomitant MTX in subjects with moderately to severely active psoriatic arthritis who have had an inadequate response or intolerance to NSAID therapy.

Study M02-570 evaluated the effectiveness and safety of adalimumab either alone or in combination with any concomitant DMARD (except cyclosporine or tacrolimus) in subjects with moderately to severely active psoriatic arthritis who have had an inadequate response to DMARD therapy.

Study M02-537 evaluates the long-term safety and efficacy of adalimumab 40 mg every other week in the treatment of psoriatic arthritis in subjects who completed the controlled Studies M02-518 and M02-570.

Study Results

Clinical Response

Studies M02-518, M02-570 and M02-537

Adalimumab was superior to placebo in all measures of disease activity ($p < 0.001$) as shown in [Table 37](#) and [Table 38](#). Among patients with psoriatic arthritis who received adalimumab, the clinical responses were apparent at the time of the first visit (Week 2), significant at Week 12, and maintained at Week 24 in the double-blind period of the study. [Table 40](#) presents data from the ongoing open-label study regarding improvement in arthritic manifestations of psoriatic arthritis.

Patients with a psoriasis involvement of at least three percent body surface area (BSA) were evaluated for Psoriatic Area and Severity Index (PASI) responses. In these patients, the skin lesions of psoriasis were improved with adalimumab, relative to placebo, as measured by the PASI. Results were similar with and without concomitant MTX therapy. The small number of patients with moderate to severe psoriasis requires additional data to adequately assess the PASI response.

Table 37 ACR and PASI Response in Placebo-Controlled Psoriatic Arthritis Study (Study M02-518) (Percent of Patients)

| Response | | Placebo N = 162 | Adalimumab [†] N = 151 |
|----------|---------|--------------------|------------------------------------|
| ACR 20 | Week 12 | 14% | 58% |
| | Week 24 | 15% | 57% |
| ACR 50 | Week 12 | 4% | 36% |
| | Week 24 | 6% | 39% |
| ACR 70 | Week 12 | 1% | 20% |
| | Week 24 | 1% | 23% |
| PASI 50 | Week 12 | 15% | 72% |
| | Week 24 | 12% | 75% |
| PASI 75 | Week 12 | 4% | 49% |
| | Week 24 | 1% | 59% |

[†] p < 0.001 for all comparisons between adalimumab and placebo

Definition(s): ACR = American College of Rheumatology; PASI = Psoriasis Area and Severity Index

Table 38 Components of Disease Activity in Psoriatic Arthritis (Study M02-518)

| Parameter mean (median) | Placebo [†] N = 162 | | Adalimumab ^{†‡} N = 151 | |
|--|---------------------------------|-------------|-------------------------------------|-------------|
| | Baseline | Week 24 | Baseline | Week 24 |
| Number of tender joints (Scale 0 to 78) | 25.8 (23.0) | 22.3 (17.0) | 23.3 (19.0) | 11.8 (5.0) |
| Number of swollen joints (Scale 0 to 76) | 14.6 (11.0) | 12.1 (8.0) | 13.4 (10.0) | 7.6 (3.0) |
| Physician global assessment ^a | 53.2 (53.0) | 46.0 (48.0) | 53.5 (54.0) | 21.4 (16.0) |
| Patient global assessment ^a | 47.2 (49.0) | 47.6 (49.0) | 47.5 (48.0) | 24.2 (18.5) |
| Pain ^a | 47.6 (47.5) | 47.9 (49.0) | 50.6 (53.0) | 25.4 (19.0) |
| Disability index (HAQ) ^b | 1.0 (1.0) | 0.9 (0.8) | 1.0 (0.9) | 0.6 (0.4) |
| CRP (mg/dL) ^c | 1.4 (0.8) | 1.4 (0.7) | 1.4 (0.8) | 0.5 (0.2) |

[†] As observed analysis presented, N at Week 24 may be less than 162 for placebo or 151 for adalimumab

[‡] p < 0.001 for adalimumab versus placebo comparisons based on mean change from baseline

^a Visual analogue scale; 0 = best, 100 = worst

^b Disability index of the Health Assessment Questionnaire (HAQ); 0 = best, 3 = worst; measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity

^c C-reactive protein (CRP) normal range: 0 to 0.287 mg/dL

Radiographic Response

Radiographic changes in the hands wrists, and feet were assessed in the psoriatic arthritis study at baseline and Week 24 during the double-blind period when patients were on adalimumab or placebo and at Week 48 when all patients were on open-label adalimumab. A modified total Sharp score (mTSS), which included distal interphalangeal joints (i.e., not identical to the TSS used for rheumatoid arthritis), was used by readers blinded to treatment group to assess the radiographs.

Week 24

The mean change in modified total Sharp score was evaluated and demonstrated that adalimumab-treated patients had significantly less progression in their X-rays, compared to placebo-treated patients. As shown in [Table 39](#), the mean change from baseline in both the erosion and the joint space narrowing scores in the adalimumab treatment group was significantly superior to placebo. As with other TNF agents, the median change in Sharp scores for both patient groups were zero.

Table 39 Radiographic Mean Changes at Week 24 in Placebo-Controlled Psoriatic Arthritis Study (Study M02-518)[†]

| Response | Placebo N = 152 | Adalimumab N = 144 | p-value |
|-------------------|--------------------|-----------------------|---------|
| Total Sharp score | 1 | -0.2 | < 0.001 |
| Erosion score | 0.6 | 0 | < 0.001 |
| JSN score | 0.4 | -0.2 | < 0.001 |

[†] Analysis of patients with X-ray films at both baseline and Week 24

Definition(s): JSN = joint space narrowing

Week 48

Adalimumab-treated patients demonstrated greater inhibition of radiographic progression at Week 48 compared to placebo-treated patients at Week 24 (see [Table 40](#)).

Table 40 Change in Modified Total Sharp Score[‡] in Psoriatic Arthritis (Study M02-537)

| Response | | Placebo N = 141 | Adalimumab N = 133 | |
|----------------------------|------------------|--------------------|-----------------------|--------------|
| | | Week 24 | Week 24 | Week 48 |
| Modified Total Sharp Score | Baseline mean | 22.1 | 23.4 | 23.4 |
| | Mean change ± SD | 0.9 ± 3.06 | -0.1 ± 1.69** | 0.1 ± 2.74** |
| | Change (range) | -3.5 to 22.0 | -6.8 to 12.5 | -5.9 to 24.2 |
| Erosion Score | Baseline mean | 11.8 | 12.4 | 12.4 |
| | Mean change ± SD | 0.5 ± 1.91 | 0.0 ± 0.91** | 0.1 ± 1.79* |
| | Change (range) | -2.2 to 14.5 | -2.2 to 7.5 | -4.4 to 16.5 |

| Response | | Placebo N = 141 | Adalimumab N = 133 | |
|-----------|------------------|--------------------|-----------------------|--------------|
| | | Week 24 | Week 24 | Week 48 |
| JSN score | Baseline mean | 10.4 | 11.0 | 11.0 |
| | Mean change ± SD | 0.4 ± 1.60 | -0.1 ± 1.06** | 0.0 ± 1.33** |
| | Change (range) | -3.5 to 10.2 | -5.7 to 5.0 | -4.0 to 7.7 |

* p < 0.05 for the difference between adalimumab, Week 48 and placebo, Week 24 (primary analysis)

** p < 0.001 for the difference between adalimumab, Week 48 and placebo, Week 24 (primary analysis)

‡ X-rays with less than 50% assessments were imputed

Definition(s): JSN = joint space narrowing; SD = standard deviation

Physical Function Response

Disability and physical function were assessed in psoriatic arthritis study using Health Assessment Questionnaire Disability Index (HAQ-DI). The adalimumab-treated patients had significantly greater improvement in the disability index of the HAQ from baseline to Week 24, compared to placebo and were maintained up to Week 84 (see [Table 41](#) and [Table 42](#)).

Table 41 Disability Index of the HAQ (Full Analysis Set) (Study M02-518)

| Disability Index of the HAQ | | Placebo N = 162 | | Adalimumab 40 mg eow N = 151 | | p-value ^a |
|-----------------------------|-----------------|--------------------|-------------|---------------------------------|-------------|----------------------|
| | | N | Mean ± SD | N | Mean ± SD | |
| Week 12 | Baseline | 154 | 1.0 | 142 | 1.0 | < 0.001* |
| | Change Observed | 154 | -0.1 ± 0.45 | 142 | -0.4 ± 0.45 | |
| Week 24 | Baseline | 145 | 1.0 | 141 | 1.0 | < 0.001* |
| | Change Observed | 145 | -0.1 ± 0.42 | 141 | -0.4 ± 0.49 | |

* Statistically significant at the p = 0.001 level

^a p-value for differences between treatment groups from an ANOVA model with treatment group and baseline methotrexate use/extent of psoriasis (≥ 3% BSA, < 3% BSA) as factors

Definition(s): HAQ = Health Assessment Questionnaire; BSA = body surface area; eow = every other week; SD = standard deviation

**Table 42 Mean Change From Baseline in Disability Index of HAQ by Visit (Observed)
(Study M02-518 Subjects Randomized to Adalimumab)**

| Visit | N | Baseline ^a Mean | Visit Mean | Change from Baseline | | |
|---------|-----|-------------------------------|------------|----------------------|-----------------------|-----------------------|
| | | | | Mean | Standard Deviation | Range (Min to Max) |
| Week 24 | 137 | 1.0 | 0.6 | -0.4 | 0.48 | -1.8 to 1.1 |
| Week 26 | 137 | 1.0 | 0.5 | -0.4 | 0.50 | -2.1 to 0.9 |
| Week 30 | 137 | 1.0 | 0.6 | -0.4 | 0.49 | -1.9 to 1.0 |
| Week 36 | 137 | 1.0 | 0.6 | -0.4 | 0.50 | -1.9 to 1.1 |
| Week 42 | 135 | 1.0 | 0.6 | -0.4 | 0.50 | -1.9 to 1.0 |
| Week 48 | 134 | 1.0 | 0.6 | -0.4 | 0.54 | -2.3 to 0.9 |
| Week 60 | 132 | 1.0 | 0.5 | -0.4 | 0.49 | -1.9 to 0.6 |
| Week 72 | 129 | 1.0 | 0.6 | -0.4 | 0.49 | -1.9 to 0.6 |
| Week 84 | 79 | 0.9 | 0.5 | -0.4 | 0.49 | -1.9 to 0.8 |

Note: The disability index of the Health Assessment Questionnaire (HAQ) has a range from 0 to 3 with a higher score indicating a greater extent of functional limitations

^a Last assessment prior to the first adalimumab injection

A subset of the subjects is still being followed in the ongoing study.

Results from the Short Form Health Survey (SF-36) support these findings, with statistically significant Physical Component Summary (PCS) scores, as well as statistically significant pain and vitality domain scores at Week 24, which were maintained to Week 72.

17.1.3 Ankylosing Spondylitis

Study Demographics and Trial Design

The safety and efficacy of adalimumab 40 mg every other week were assessed in 393 adult patients in two randomized, 24-week double-blind, placebo-controlled studies in patients with active ankylosing spondylitis who have had an inadequate response to or intolerance to one or more NSAIDs, and who may have additionally failed DMARD therapy. The larger study enrolled 315 adult patients with active ankylosing spondylitis [defined as fulfilling at least two of the following three criteria: (1) a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4 cm, (2) a visual analogue score (VAS) for total back pain ≥ 40 mm, and (3) morning stiffness ≥ 1 hour]. The primary efficacy endpoint was percentage of ASAS 20 responders at Week 12 measured by the Assessment in Ankylosing Spondylitis (ASAS) response criteria. Additional pre-determined endpoints included: response as defined by ASAS 5/6 criteria, ASAS 40/50/70 and partial remission, Bath Ankylosing Spondylitis Metrology Index (BASMI), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). The blinded period was followed by an open-label period during which patients received adalimumab 40 mg every other week subcutaneously for up to an additional 80 weeks.

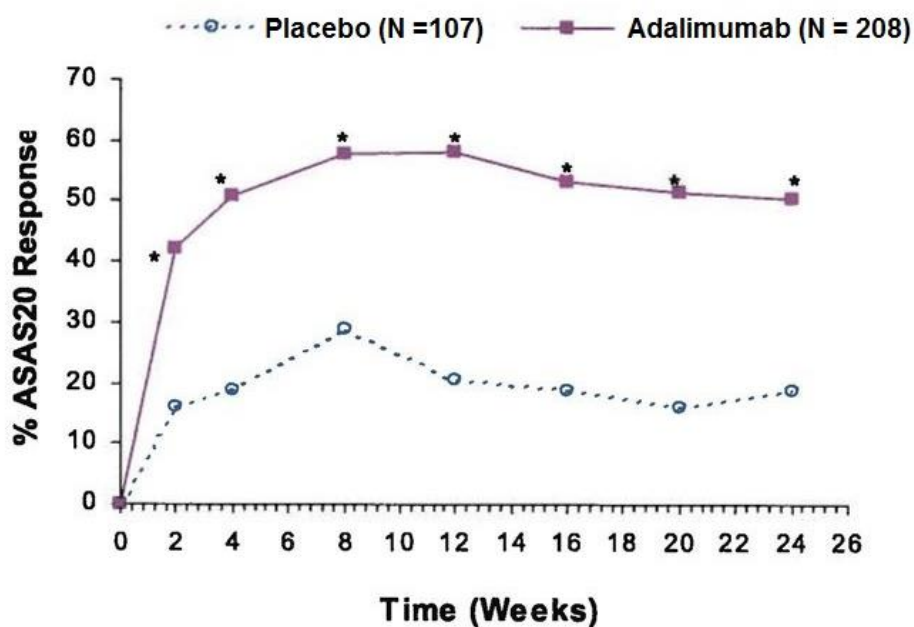
Study Results

Clinical Response

Results showed statistically significant reduction in signs and symptoms of ankylosing spondylitis in patients treated with adalimumab compared to placebo in Study M03-607. Significant improvement in measures of disease activity was first observed at Week 2 and maintained through Week 24 as shown in Figure 3 and Table 43.

Patients with total spinal ankylosis were included in the larger study (n = 11). Responses of these patients were similar to those without total ankylosis.

Figure 3. ASAS 20 Response by Visit, Study M03-607



* p<0.001 level versus placebo

At Week 12, the ASAS 20/50/70 responses were achieved by 58, 38, and 23%, respectively, of patients receiving adalimumab, compared to 21, 10, and 5% respectively, of patients receiving placebo (p < 0.001). At Week 24, the ASAS 20/50/70 responses were achieved by 51, 35 and 24%, respectively, of patients receiving adalimumab, compared to 19, 11, and 8%, respectively, of patients receiving placebo (p < 0.001). These results were sustained in patients receiving open-label adalimumab through Week 52.

In a sub-group analysis by region an adalimumab versus placebo treatment group difference was observed between the US and EU subjects (21.7 and 50.9% respectively). This difference in the treatment effect is driven by the different placebo ASAS 20 response rates (33.3% for US versus 10.2% for EU). However, the adalimumab ASAS 20 response rates were 55 and 61.1% in the US and EU respectively.

A low level of disease activity [defined as a value < 20 (on a scale of 0 to 100 mm) in each of the four ASAS response parameters] was achieved at Week 24 in 22% of adalimumab-treated patients versus 6% in placebo-treated patients (p < 0.001).

Other secondary and additional measures of efficacy such as response as defined by ASAS 5/6 criteria, ASAS 40, metrology (BASMI), enthesitis (MASES), and disease activity (BASDAI) were statistically significant at Weeks 12 and 24.

Table 43 Components of Ankylosing Spondylitis Disease Activity in Study M03-607

| Parameters | Placebo N = 107 | | Adalimumab N = 208 | |
|--|--------------------|-----------------|-----------------------|-----------------|
| | Baseline Mean | Week 24 Mean | Baseline Mean | Week 24 Mean |
| ASAS 20 Response Criteria* | | | | |
| Patient's Global Assessment of Disease Activity ^a | 65 | 60 | 63 | 38 |
| Total Back Pain | 67 | 58 | 65 | 37 |
| Inflammation ^b | 6.7 | 5.6 | 6.7 | 3.6 |
| BASFI | 56 | 51 | 52 | 34 |
| BASDAI* Score | 6.3 | 5.5 | 6.3 | 3.7 |
| CRP* | 2.2 | 2 | 1.8 | 0.6 |

^a Percent of subjects with at least a 20% and 10-unit improvement measured on a visual analogue scale (VAS) with 0 = "none" and 100 = "severe"

^b Mean of questions 5 and 6 of BASDAI

* Statistically significant as $p < 0.001$ for all comparisons between adalimumab and placebo at Week 24

Definition(s): BASFI = Bath Ankylosing Spondylitis Functional Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CRP = C-reactive protein (mg/dL)

Similar results (not all statistically significant) were seen in the second randomized trial, a multicenter, double-blind, placebo-controlled study of 82 patients with ankylosing spondylitis (Study M03-606).

Patients treated with adalimumab achieved statistically significant greater improvement from baseline in the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) score (-3.15 versus -0.95, $p < 0.001$) and in the Short Form Health Survey (SF-36) Physical Component Summary (PCS) score (6.93 versus 1.55, $p < 0.001$) compared to placebo-treated patients at Week 12, which were maintained through Week 24.

17.1.4 Crohn's Disease

Study Demographics and Trial Design

The safety and efficacy of multiple doses of adalimumab were assessed in over 1,500 adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] ≥ 220 and ≤ 450) in randomized, double-blind, placebo-controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted and 80% of patients continued to receive at least one of these medications.

[Table 44](#) summarizes the controlled clinical trials and [Table 45](#) summarizes the open-label clinical trials that were done in patients with moderately to severely active Crohn's disease.

Table 44 Summary of Controlled Clinical Trials Supporting Safety and Efficacy in Patients with Crohn's Disease

| Study # | Trial Design | Dosage, Route of Administration and Duration | Study Subjects (n) | Mean Age (Range) | Gender (% Female) |
|------------------|---|---|--------------------|------------------------|-------------------|
| M02-403 (CD I) | Randomized, double-blind, placebo-controlled, multicenter, dose ranging study in anti-TNF naïve patients | Adalimumab 160 mg at Week 0 and 80 mg at Week 2; or Adalimumab 80 mg at Week 0 and 40 mg at Week 2; or Adalimumab 40 mg at Week 0 and 20 mg at Week 2 | 225 | 39 ± 12 (18 to 74) | 55.6 |
| | | Placebo Subcutaneous 4 weeks | 74 | 37 ± 13 (19 to 74) | 50.0 |
| M04-691 (CD II) | Randomized, double-blind, placebo-controlled, multicenter study in patients who had lost response to or were intolerant to infliximab | Adalimumab 160 mg at Week 0 and 80 mg at Week 2 | 159 | 39.4 ± 11.9 (19 to 75) | 68.6 |
| | | Placebo Subcutaneous 4 weeks | 166 | 37.4 ± 11.9 (18 to 75) | 60.8 |
| M02-404 (CD III) | Randomized, double-blind, multicenter, placebo-controlled | Initial Open-Label: Adalimumab 80 mg at Week 0 and 40 mg at Week 2 | | | |
| | | Post-Randomization (Week 4): Adalimumab 40 mg eow | 260 | 36.8 ± 11.5 (17 to 73) | 62.7 |
| | | Adalimumab 40 mg ew | 257 | 37.8 ± 12.1 (18 to 75) | 61.1 |
| | | Placebo | 261 | 36.9 ± 11.4 (18 to 75) | 62.1 |
| | | Not randomized Subcutaneous 56 weeks | 76 | 36.1 ± 13.6 (19 to 75) | 60.5 |

| Study # | Trial Design | Dosage, Route of Administration and Duration | Study Subjects (n) | Mean Age (Range) | Gender (% Female) |
|-----------------|---|--|--------------------|--------------------------------|-------------------|
| M05-769 (CD VI) | Randomized, double-blind, placebo-controlled, multicenter, efficacy and safety study. | Patients received OL induction therapy of adalimumab 160/80 mg at Weeks 0/2, and were stratified by responder status to adalimumab 40 mg eow or placebo for up to 52 weeks. At Week 52, patients were switched to OL adalimumab 40 mg eow for up to an additional 36 weeks.) | | | |
| | | Adalimumab eow Placebo | 64 65 | 37 (18 to 74) 37 (18 to 67) | 62.5 63.1 |

Definition(s): ew = every week; eow = every other week; TNF = tumor necrosis factor; OL =open-label

Table 45 Summary of Open-Label Clinical Trials Supporting Safety and Efficacy in Patients with Crohn’s Disease

| Study # | Trial Design | Dosage, Route of Administration and Duration | Study Subjects (n) | Mean Age (Range) | Gender (% Female) |
|-----------------|--|--|--------------------|------------------|-------------------|
| M02-433 (CD IV) | Open-label extension of placebo-controlled Study M02-403 | Patients received OL adalimumab 40 mg at baseline (Week 0) and week 2. At Week 4, patients were assigned to one of three blinded treatment groups (adalimumab eow, ew, or placebo) or OL adalimumab eow treatment, based on clinical remission status at baseline. After 1 year (Week 56), patients entered long-term extension phase up to more than 5 years (including preceding M02-403 study); those receiving blinded treatment were switched to OL adalimumab eow, and those in the OL group continued their OL treatment. | | | |
| | | All | 276 | 39 (18 – 74) | 54.7 |

| Study # | Trial Design | Dosage, Route of Administration and Duration | Study Subjects (n) | Mean Age (Range) | Gender (% Female) |
|----------------|---|---|--------------------|-------------------------|-------------------|
| M04-690 (CD V) | Open-label extension of placebo-controlled Studies M04-691 or M02-404 | Patients entering from a blinded cohort were assigned to OL adalimumab 40 mg eow; patients entering the study from an OL cohort continued their previous dosing regimen of eow or ew. Study M02-404 cohort Study M04-691 cohort | 467 310 | All 38 (17 to 75) | All 62.4 |

Definition(s): ew = every week; eow = every other week; OL =open-label

Description of Clinical Studies

Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies, Studies M02-403 and M04-691.

In Study M02-403, 299 TNF-blocker naïve patients were randomized to one of four treatment groups; the placebo group received placebo at Weeks 0 and 2, the 160/80 group received 160 mg adalimumab at Week 0 and 80 mg at Week 2, the 80/40 group received 80 mg at Week 0 and 40 mg at Week 2, and the 40/20 group received 40 mg at Week 0 and 20 mg at Week 2.

In Study M04-691, 325 patients who had lost response or were intolerant to infliximab were randomized to receive either 160 mg adalimumab at Week 0 and 80 mg at Week 2 or placebo at Weeks 0 and 2.

Maintenance of clinical remission was evaluated in Study M02-404.

In Study M02-404, 854 patients received open-label 80 mg adalimumab at Week 0 and adalimumab 40 mg at Week 2. At Week 4, patients were stratified by their responder status and previous anti-tumor necrosis factor (TNF) use (no, yes) and randomized to one of three blinded treatment groups: adalimumab 40 mg every other week, adalimumab 40 mg every week or placebo with a total study duration of 56 weeks. Patients in clinical response (decrease in CDAI \geq 70) at Week 4 were stratified and analyzed separately from those not in clinical response at Week 4. Corticosteroid tapering was permitted after Week 8.

Study M05-769 assessed mucosal healing in 135 patients; patients received open-label induction therapy of adalimumab 160/80 mg at weeks 0/2, and were stratified by responder status to adalimumab 40 mg every other week (eow) or placebo for up to 52 weeks. At Week 52, patients were switched to open-label adalimumab 40 mg eow for up to an additional 36 weeks.

Study Results

Clinical Responses

Studies M02-403 and M04-691

A statistically significantly greater percentage of the patients treated with adalimumab 160/80 mg achieved induction of clinical remission versus placebo at Week 4 regardless of whether the patients were TNF-blocker naïve (Study M02-403) or had lost response or are intolerant to infliximab (Study M04-691) ([Table 46](#) and [Table 47](#), respectively).

The percentage of subjects who achieved clinical remission with adalimumab 160/80 mg induction therapy was greater for those receiving corticosteroids versus those who did not.

Table 46 Induction of Clinical Remission and Response in Infliximab Naïve Patients (Study M02-403) (Percent of Patients)

| Response | | Placebo N = 74 | Adalimumab 160/80 mg N = 76 |
|----------|--|-------------------|-----------------------------------|
| Week 4 | Clinical remission Difference ^a (95% CI) | 12% | 36%* 23.4 (10.3, 36.4) |
| | Clinical response (CR-100) Difference ^a (95% CI) | 24% | 49%** 24.4 (9.5, 39.3) |
| | Clinical response (CR-70) Difference ^a (95% CI) | 34% | 58%** 24.1 (8.6, 39.6) |

All p-values are pairwise comparisons of proportions for adalimumab versus placebo

* p < 0.001

** p < 0.01

^a Difference refers to the difference between the proportion (%) of adalimumab-treated subjects achieving clinical remission and clinical response compared with the placebo-treated subjects; 95% CI based on normal approximation of the binomial

Definition(s): CI = confidence interval; Clinical remission = Crohn's Disease Activity Index (CDAI) score < 150; Clinical response 100 (CR-100) and a clinical response 70 (CR-70) = decreases from baseline in CDAI Clinical response 100 (CR-100) and a clinical response 70 (CR-70) = decreases from baseline in CDAI scores of at least 100 points and at least 70 points, respectively

Table 47 Induction of Clinical Remission and Response in Infliximab Experienced Patients (Study M04-691) (Percent of Patients)

| Response | | Placebo N = 166 | Adalimumab 160/80 mg N = 159 |
|----------|--|--------------------|------------------------------------|
| Week 4 | Clinical remission Difference ^a (95% CI) | 7% | 21%*14.2 (6.7, 21.6) |
| | Clinical response (CR-100) Difference ^a (95% CI) | 25% | 38%**13.7 (3.7, 23.7) |
| | Clinical response (CR-70) Difference ^a (95% CI) | 34% | 52%**17.8 (7.3, 28.4) |

p-values are pairwise comparisons of proportions for adalimumab versus placebo

* p < 0.001

** p < 0.01

^a Difference refers to the difference between the proportion (%) of adalimumab-treated subjects achieving clinical remission and clinical response compared with the placebo-treated subjects; 95% CI based on normal approximation of the binomial

Definition(s): CI = confidence interval; Clinical remission = Crohn's Disease Activity Index (CDAI) score < 150; Clinical response 100 (CR-100) and a clinical response 70 (CR-70) = decreases from baseline in CDAI scores of at least 100 points and at least 70 points, respectively scores of at least 100 points and at least 70 points, respectively

Clinical Remission at Week 4 by baseline predictors in infliximab experienced patients is presented in [Table 48](#).

Table 48 Clinical Remission at Week 4 by Baseline Predictors in Infliximab Experienced Patients (Study M04-691)

| Baseline Predictors | | Placebo N = 166 | Adalimumab 160/80 mg N = 159 |
|-------------------------|-------|--------------------|---------------------------------|
| Corticosteroid User | | 3/73 (4.1) | 18/55 (32.7) |
| Corticosteroid Nonuser | | 9/93 (9.7) | 16/104 (15.4) |
| Aminosalicylate User | | 6/60 (10.0) | 6/45 (13.3) |
| Aminosalicylate Nonuser | | 6/106 (5.7) | 28/114 (24.6) |
| CDAI Score | ≤ 300 | 8/81 (9.9) | 24/75 (32.0) |
| | > 300 | 4/85 (4.7) | 10/84 (11.9) |

Definition(s): CDAI = Crohn's disease activity index

Study M02-404

At Week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. Of those in clinical response at Week 4, 48% had been previously exposed to other anti-TNF therapy. At Weeks 26 and 56, statistically significantly greater proportions of patients who were in clinical response at Week 4 achieved clinical remission in the adalimumab maintenance groups compared to patients in the placebo maintenance group ([Table 49](#)).

Table 49 Maintenance of Clinical Remission and Response (Percent of Patients) (Study M02-404)

| Response | | Placebo N = 170 | Adalimumab 40 mg eow N = 172 | Adalimumab 40 mg ew N = 157 |
|----------|--|--------------------|------------------------------------|-----------------------------------|
| Week 26 | Clinical remission Difference ^a (95% CI) | 17% | 40%*22.5 (13.2, 31.7) | 47%* 29.4 (19.8, 39.1) |
| | Clinical response (CR-100) Difference ^a (95% CI) | 27% | 52%*25.3 (15.3, 35.3) | 52%* 25.8 (15.5, 36.0) |
| | Clinical response (CR-70) Difference ^a (95% CI) | 28% | 54%*25.8 (15.8, 35.9) | 56%* 27.8 (17.5, 38.1) |
| Week 56 | Clinical remission Difference ^a (95% CI) | 12% | 36%*24.3 (15.6, 32.9) | 41%* 29.6 (20.5, 38.7) |
| | Clinical response (CR-100) Difference ^a (95% CI) | 17% | 41%*24.8 (15.6, 34.0) | 48%* 31.3 (21.7, 40.9) |
| | Clinical response (CR-70) Difference ^a (95% CI) | 18% | 43%*25.4 (16.9, 34.7) | 49%* 31.4 (21.7, 41.1) |

* p < 0.001 for adalimumab versus placebo pairwise comparisons of proportions

^a Difference refers to the difference between the proportion (%) of adalimumab-treated subjects achieving clinical remission and clinical response compared with the placebo-treated subjects; 95% CI based on normal approximation of the binomial

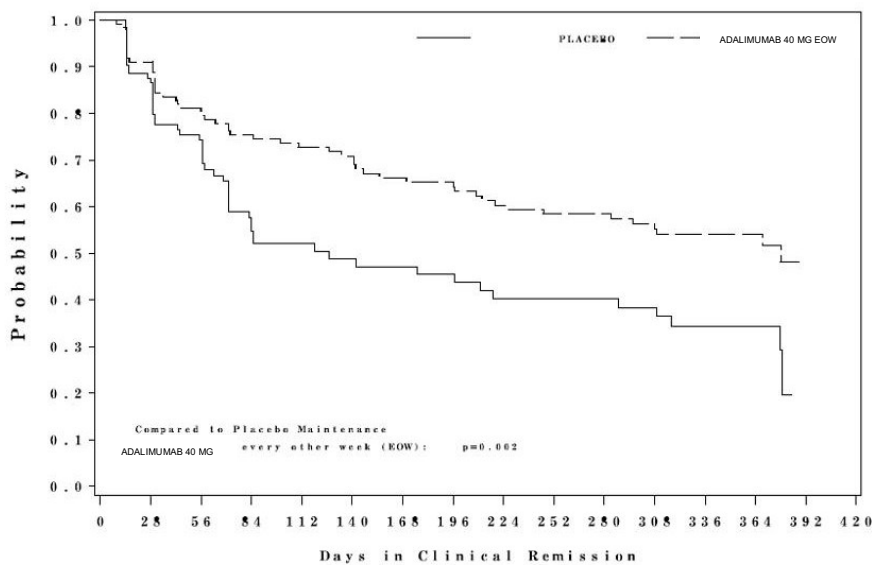
Definition(s): eow = every other week; ew = every week; CI = confidence interval; Clinical remission = Crohn's Disease Activity Index (CDAI) score < 150; Clinical response 100 (CR-100) and clinical response 70 (CR-70) = decreases from baseline in CDAI scores of at least 100 points and at least 70 points, respectively

More patients receiving adalimumab maintenance therapy were able to achieve remission and discontinue corticosteroids for at least 90 days than those receiving placebo at Week 26 (19% adalimumab every other week and 15% adalimumab every week versus 3% placebo, $p < 0.02$) and at Week 56 (29% adalimumab every other week and 20% adalimumab every week versus 5% placebo, $p < 0.01$).

In Study M02-404, 117 patients had at least one draining fistula at Baseline and Screening. Of those, 23 out of 70 in the adalimumab group (both regimens) and 6 out of 47 in the placebo group had no draining fistula at the last two evaluations.

Of those in response at Week 4 who attained remission during the study, patients in the adalimumab maintenance groups maintained remission for a significantly longer time than patients in the placebo maintenance group (Figure 4).

Figure 4 Days in Clinical Remission for Patients Who Had Achieved Clinical Remission (Induction Period) by Week 4 in Study M02-404



Some patients who experience decrease in their response may benefit from an increase in dose to adalimumab 40 mg every week. Supportive evidence for a restoration of clinical response as a result of dose escalation was derived from the modified-intent-to treat (mITT) Analysis Set of Study M02-404 in subjects who initially responded but lost response to adalimumab 40 mg every other week dosing. In those subjects who responded at Week 4, were in remission at Week 12 but lost remission after Week 12, and were dose escalated to adalimumab 40 mg every week ($n = 14$), clinical remission was restored in 71% (10/14) of these subjects, with median time to restored clinical remission of 9 weeks.

Some patients who have not responded by Week 4 (induction period) may benefit from continued maintenance therapy through Week 12. Available data suggest that the clinical response is usually achieved at Week 4 of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Symptoms, overall well-being and functioning were assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ). Treatment with adalimumab resulted in statistically significant improvements in IBDQ total score which measures bowel symptoms, systemic symptoms, emotional well-being and social functioning, compared with placebo ($p < 0.001$) at Week 4 in Studies M02-403 and M04-691 and Weeks 26 and 56 in Study M02-404.

Study M05-769

An endoscopy study ($n = 135$) assessed rates of mucosal healing in patients with moderate to severe Crohn's Disease given either adalimumab or placebo. After 8 weeks of randomized treatment (Week 12 of study), although the results were not statistically significant ($p = 0.056$), there was a trend towards higher levels of mucosal healing in subjects given adalimumab compared with subjects given placebo (mucosal healing in 27.4% (17/62) adalimumab vs 13.1% (8/61) given placebo. In this study, the placebo group received open-label adalimumab induction therapy.

17.1.5 Ulcerative Colitis

Study Demographics and Trial Design

The safety and efficacy of multiple doses of adalimumab were assessed in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 on a scale of 0 to 12 points, with an endoscopy subscore of 2 to 3 on a scale of 0 to 3) despite concurrent or prior treatment with immunosuppressants such as corticosteroids, azathioprine, or 6-MP in two randomized, double-blind, placebo-controlled studies (M06-826 and M06-827) and an open-label extension study. Both studies M06-826 and M06-827 enrolled TNF-blocker naïve patients, but M06-827 also allowed entry of patients who lost response or were intolerant to TNF-blockers. Forty percent (40%) of patients enrolled in Study M06-827 had previously used another TNF-blocker.

Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted. In Studies M06-826 and M06-827, patients were receiving aminosalicylates (69%), corticosteroids (59%) and/or azathioprine or 6-MP (37%) at baseline. In both studies, 92% of patients continued to receive at least one of these medications.

[Table 50](#) summarizes the controlled clinical trials and [Table 51](#) summarizes the open-label clinical trial that were done in patients with ulcerative colitis.

Table 50 Summary of Controlled Clinical Trials Supporting Safety and Efficacy in Patients with Ulcerative Colitis

| Study # | Trial Design | Dosage, Route of Administration and Duration | Study Subjects (n) | Mean Age (Range) | Gender (% Female) |
|----------------------------------|--|--|--------------------|-----------------------|-------------------|
| M06-826 (UC I) (ULTRA I) | Randomized, double-blind (Weeks 0 to 8), placebo-controlled, multicenter induction study followed by an open-label extension (Weeks 8 to 52) in anti- TNF naïve subjects | Adalimumab 160 mg at Week 0, 80 mg at Week 2, and 40 mg eow starting at Week 4 | 223* | 38 ± 13 (18 to 75) | 38.1 |
| | | Adalimumab 80 mg at Week 0 and 40 mg eow starting at Week 2 | 130 | 42 ± 14 (18 to 75) | 40.0 |
| | | Placebo Subcutaneous 52 weeks | 222* | 40 ± 13 (18 to 74) | 37.4 |
| M06-827 (UC II) (ULTRA II) | Randomized, double-blind, placebo-controlled, multicenter induction and maintenance study | Adalimumab 160 mg at Week 0, 80 mg at Week 2, and 40 mg eow starting at Week 4 | 248 | 40 ± 12 (18 to 72) | 42.7 |
| | | Placebo Subcutaneous 52 weeks | 246 | 41 ± 13 (18 to 79) | 38.2 |

* 130 subjects were randomized for the primary efficacy analysis

Definition(s): ew = every week; eow = every other week

Table 51 Summary of Open-Label Clinical Trials Supporting Safety and Efficacy in Patients with Ulcerative Colitis

| Study # | Trial Design | Dosage, Route of Administration and Duration | Study Subjects (n) | Mean Age (Range) | Gender (% Female) |
|---------------------|--|---|--------------------|-----------------------|-------------------|
| M10-223 (UC III) | Open-label extension of controlled Studies M06-826 and M06-827 | Patients entering the study from a blinded cohort were assigned to adalimumab 40 mg eow; those entering the study from an open-label cohort continued their previous dosing regimen of adalimumab 40 mg eow or ew. Subcutaneous up to 292 weeks | 498 | 42 ± 13 (19 to 76) | 36.9 |

Definition(s): ew = every week; eow = every other week

Description of Clinical Studies

Induction of clinical remission (defined as Mayo score ≤ 2 with no individual subscore > 1) at Week 8 was evaluated in Study M06-826. In Study M06-826, 390 TNF-blocker naïve patients were randomized to one of three treatment groups for the primary efficacy analysis. The placebo group received placebo at Week 0, 2, 4 and 6. The 160/80 group received 160 mg adalimumab at Week 0 and 80 mg at Week 2, and the 80/40 group received 80 mg adalimumab at Week 0 and 40 mg at Week 2. After Week 2, patients in both adalimumab treatment groups received 40 mg every other week (eow). Clinical remission was assessed at Week 8.

Induction of clinical remission at Week 8, clinical remission at Week 52 and sustained clinical remission (defined as clinical remission at both Weeks 8 and 52) were studied in Study M06-827. In Study M06-827, 518 patients were randomized to receive either adalimumab 160 mg at Week 0, 80 mg at Week 2, and 40 mg eow starting at Week 4 through Week 50, or placebo starting at Week 0 and eow through Week 50. Corticosteroid taper was permitted starting at Week 8.

Study Results

Clinical Responses

In both Studies M06-826 and M06-827, a greater proportion of subjects induced with 160/80 mg adalimumab achieved clinical remission versus placebo at Week 8 ([Table 52](#)). In Study M06-826, there was no statistically significant difference in clinical remission observed between the adalimumab 80/40 mg group and the placebo group at Week 8 and no statistically significant difference in clinical response or mucosal healing observed between the adalimumab 160/80 mg group and the placebo group at Week 8. Response at Week 8 was achieved by 54.6% (71/130) in the adalimumab 160/80 mg group and 44.6% (58/130) in the placebo group with a treatment difference and 95% confidence interval (CI) of 10.0% (-2.1, 22.1). Mucosal healing at Week 8 was achieved by 46.9% (61/130) in the adalimumab group and 41.5% (54/130) in the placebo group with a treatment difference and 95% CI of 5.4% (-6.7, 17.4).

In Study M06-827 clinical remission at Week 52 was a co-primary endpoint, achieved by 17.3% (43/248) of the adalimumab group and 8.5% (21/246) of the placebo group. Sustained clinical remission (at both Weeks 8 and 52) was achieved by 8.5% (21/248) of the adalimumab group and 4.1% (10/246) of the placebo group. Among those treated with adalimumab who were in remission at Week 8, 51% (21/41) were in remission at Week 52. In the adalimumab group 46.8% (116/248) patients moved to open label escape therapy for lack of response and 54.9% (135/246) patients in the placebo group. During the double-blind period, 5.6% (14/248) in the adalimumab group and 7.7% (19/246) in the placebo group withdrew without final evaluation due to non-colitis related reasons (not lack of efficacy or colitis related adverse event). In the adalimumab group 79 (31.9%) patients completed the Week 8 and 52 visits and 56 (22.8%) patients in the placebo group.

Response at Week 8 and at Week 52 were achieved in 50.4% (125/248) and 30.2% (75/248) of the adalimumab group and 34.6% (85/246) and 18.3% (45/246) in the placebo group respectively with a treatment difference and 95% CI of 15.9% (7.0, 24.2) and 11.9% (4.3, 19.2). Sustained response (at both Weeks 8 and 52) was achieved by 23.8% (59/248) of the adalimumab group and 12.2% (30/246) of the placebo group with a treatment difference and 95% CI of 11.6% (4.7, 18.1).

Mucosal healing (endoscopic improvement of the mucosa) at Week 8 and at Week 52 were achieved in 41.1% (102/248) and 25.0% (62/248) in the adalimumab group and 31.7% (78/246) and 15.4% (38/246) of the placebo group with a treatment difference and 95% CI of 9.4% (0.8, 17.6) and 9.6% (2.3, 16.4). Sustained mucosal healing (at both Weeks 8 and 52) was

achieved by 18.5% (46/248) of the adalimumab group and 10.6% (26/246) of the placebo group with a treatment difference and 95% CI of 8.0% (1.6, 14.0).

In the adalimumab group, 13.3% (20/150) of the patients who were on corticosteroids at baseline were able to discontinue corticosteroids before Week 52 and achieved remission at Week 52 compared to 5.7% (8/140) in the placebo group.

Table 52 Study M06-826 and M06-827: Summary of Results of Primary and Ranked Co-Primary and Ranked Secondary Endpoints

| Analysis ^a | Placebo | Adalimumab 160/80/40 | Treatment Difference (95% CI) |
|------------------------------------|---------|-------------------------|-------------------------------------|
| Study M06-826 | N = 130 | N = 130 | |
| Primary Endpoint | | | |
| Clinical remission at Week 8 | 9.2% | 18.5%* | 9.2 (0.9, 17.6) |
| Study M06-827 | N = 246 | N = 248 | |
| Ranked Co-Primary Endpoints | | | |
| 1. Remission at Week 8 | 9.3% | 16.5%* | 7.2 (1.2, 12.9) |
| 2. Remission at Week 52 | 8.5% | 17.3%* | 8.8 (2.8, 14.5) |

Note: According to the NRI method, all missing remission values were considered to be non-remission. Subjects who switched to OL adalimumab were considered to be non-remitters at and after the time of the switch.

Clinical remission per Mayo score: Mayo score \geq 2 with no individual subscore $>$ 1

Mayo score consists of four subscores (stool frequency [SFS], rectal bleeding [RBS], findings of endoscopy, and physician's global assessment). Mayo scores range from 0-12.

*p<0.05 for adalimumab vs. placebo pairwise comparison of proportions

In the subgroup of patients in Study M06-827 with prior TNF-blocker use, the treatment difference for induction of clinical remission was lower than that seen in the whole study population, and the treatment differences for sustained clinical remission and clinical remission at Week 52 appeared to be similar to those seen in the whole study population.

17.1.6 Hidradenitis Suppurativa

Study Demographics and Trial Design

The safety and efficacy of adalimumab were assessed in two randomized, double-blind, placebo-controlled studies in adult patients with moderate to severe hidradenitis suppurativa who were intolerant, had a contraindication or an inadequate response to systemic antibiotic therapy. In both studies, patients had Hurley Stage II or III disease with at least 3 abscesses or inflammatory nodules. [Table 53](#) summarizes the clinical trials in patients with moderate to severe hidradenitis suppurativa.

Table 53 Summary of Clinical Trials Evaluating Safety and Efficacy in Patients with Hidradenitis Suppurativa

| Study # | Trial Design | Dosage, Route of Administration and Duration | Study Subjects (n) | Mean Age (Range) | Gender (% Female) |
|----------------------|--|---|--------------------|--------------------|-------------------|
| M11-313 (PIONEER I) | Randomized, double-blind, placebo-controlled, 2-period | <p><u>Period A - 12 weeks</u> adalimumab 160 mg at Week 0, 80 mg at Week 2, then 40 mg ew from Week 4 to Week 11; Placebo</p> <p><u>Period B - 24 weeks</u> adalimumab 40 mg ew; adalimumab 40 mg eow; Placebo</p> <p>Subcutaneous 36 weeks</p> | 307 | 37.0 (18 to 67) | 63.8 |
| M11-810 (PIONEER II) | Randomized, double-blind, placebo-controlled, 2-period | <p><u>Period A - 12 weeks</u> adalimumab 160 mg at Week 0, 80 mg at Week 2, then 40 mg ew from Week 4 to Week 11; Placebo</p> <p><u>Period B - 24 weeks</u> adalimumab 40 mg ew; adalimumab 40 mg eow; Placebo</p> <p>Subcutaneous 36 weeks</p> | 326 | 35.5 (18 to 69) | 67.8 |

Definition(s): ew = every week; eow = every other week

Description of Clinical Studies

Both studies consisted of an initial 12-week double-blind treatment period (Period A), and a subsequent 24-week double-blind treatment period (Period B). In Period A, patients received placebo or adalimumab at an initial dose of 160 mg at Week 0, 80 mg at Week 2, and 40 mg every week starting at Week 4 to Week 11. After 12 weeks of therapy, patients who had received adalimumab in Period A were re-randomized in Period B to 1 of 3 treatment groups (adalimumab 40 mg every week, adalimumab 40 mg every other week, or placebo from Week 12 to Week 35). In Period B, patients who had been randomized to placebo in Period A were assigned to receive adalimumab 40 mg every week (M11-313) or placebo (M11-810) in a blinded fashion. In both studies, the randomization in Period A was to be stratified by baseline Hurley Stage (II versus III). A subject's Hurley Stage was determined by the worst Hurley Stage

across all affected anatomic regions. Baseline concomitant antibiotic use (yes versus no) was an additional randomization factor in Study M11-810.

Both studies evaluated Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12 as the primary endpoint. Reduction of inflammatory lesions and prevention of worsening of abscesses and draining fistulas was assessed using HiSCR which was defined as achieving at least a 50% reduction from baseline in AN [total abscess and inflammatory nodule] count plus no increase in abscess count and no increase in draining fistula count relative to baseline. Reduction in hidradenitis suppurativa-related skin pain was assessed using a Numeric Rating Scale in patients who entered the study with an initial baseline score of 3 or greater on a 11 point scale.

The majority of patients were female, obese (≥ 90 kg, BMI ≥ 30), current smokers, and had hidradenitis suppurativa disease duration of over 9 years; the patients had a mean modified Sartorius Score of 131.6, AN count of 12.8, and draining fistula count of 3.8.

Patients participating in Studies M11-313 and M11-810 were eligible to enroll into an open-label extension study (Study M12-555) in which adalimumab 40 mg was administered every week. Study M12-555 aimed to determine the long-term safety, tolerability and efficacy of adalimumab in subjects with moderate to severe hidradenitis suppurativa for at least 60 weeks.

Throughout all 3 studies, patients used topical antiseptic wash daily.

Study Results

Clinical Responses

Studies M11-313 and M11-810

In Period A of Studies M11-313 and M11-810, 40 mg of adalimumab treatment every week resulted in statistically significant greater proportion of patients achieving HiSCR at Week 12 in subjects with moderate to severe hidradenitis suppurativa compared with placebo. Results are shown in [Table 54](#).

Table 54 Clinical Response at 12 Weeks, M11-313 and M11-810

| Endpoint | M11-313 (PIONEER I) | | M11-810 (PIONEER II) | |
|--|-----------------------|-------------------------|-----------------------|-------------------------|
| | Placebo | adalimumab 40 mg weekly | Placebo | adalimumab 40 mg weekly |
| Hidradenitis Suppurativa Clinical Response (HiSCR) | N = 154 40 (26.0%) | N = 153 64 (41.8%) | N = 163 45 (27.6%) | N = 163 96 (58.9%) |
| Difference (95% CI) ^a | 15.9 % (5.3%, 26.5%) | | 31.5% (20.7%, 42.2%) | |
| P-value ^b | 0.003 | | < 0.001 | |

^a 95% CI for stratum-adjusted difference was calculated according to the extended Mantel-Haenszel statistic for the comparison of two treatment groups, adjusting for baseline Hurley Stage (II/III) in M11-313 and adjusting for baseline Hurley Stage (II/III) and baseline antibiotic use (Yes/No) in M11-810.

^b P-value was calculated from the Cochran-Mantel-Haenszel test adjusting for baseline Hurley Stage (II/III) in M11-313, and adjusting for baseline Hurley Stage (II/III) and baseline antibiotic use (Yes/No) in M11-810.

At Week 12, a significantly higher proportion of patients treated with adalimumab in Study M11-810 experienced at least a 30% decrease in hidradenitis suppurativa-related skin pain versus placebo (45.7% vs 20.7%, $P < 0.001$), whereas the difference was not significant in Study M11-313 (27.9% vs 24.8%, $P = 0.628$). During the initial 12 weeks of treatment, 13.7% of patients treated with adalimumab experienced flare compared to 35.7% in the placebo group in

Study M11-313. The corresponding observed percentage was 11.0% and 35.0% for the adalimumab and placebo group, respectively, in Study M11-810.

Among patients who were randomized to adalimumab in Period A, achieved HiSCR at Week 12, and re-randomized to adalimumab every week (N = 52), adalimumab every other week (N = 52) and placebo (N = 53), 24 (46.2%), 22 (42.3%), and 32 (60.4%) discontinued prior to Week 36, respectively; 17 (32.7%), 20 (38.5%), and 27 (50.9%) discontinued primarily due to experiencing protocol specified loss of response.

In patients with at least a partial response ($\geq 25\%$ improvement in AN count) to adalimumab 40 mg weekly at Week 12, the proportion of patients achieving HiSCR at Week 24 was 57.1% in adalimumab 40 mg weekly, 51.4% in adalimumab 40 mg every other week and 32.9% in the placebo group. The corresponding proportion at Week 36 was 55.7% in adalimumab 40 mg weekly, 40.0% in adalimumab 40 mg every other week and 30.1% in the placebo group.

17.1.7 Psoriasis

Study Demographics and Trial Design

The safety and efficacy of adalimumab were assessed in over 1,600 patients 18 years of age or older with moderate to severe chronic plaque psoriasis who were candidates for systemic therapy or phototherapy in randomized, double-blind, well-controlled studies.

[Table 55](#) summarizes the controlled clinical trials that were done in patients with moderate to severe plaque psoriasis.

Table 55 Summary of Controlled Clinical Trials Supporting Safety and Efficacy in Patients with Psoriasis

| Study # | Trial Design | Dosage, Route of Administration and Duration | Study Subjects (n) | Mean Age (Range) | Gender (% Female) |
|------------------|---|--|--------------------|------------------|-------------------|
| M03-656 (Ps I) | <p><u>Period A:</u> Double-blind, placebo-controlled treatment period in patients with moderate to severe chronic plaque psoriasis (PASI \geq 12, BSA \geq 10%); patients were randomly assigned (2:1) to receive adalimumab or placebo</p> <p><u>Period B:</u> Open-label treatment period; all patients who achieved a \geq PASI 75 response at Week 16 received adalimumab</p> <p><u>Period C:</u> Double-blind, placebo-controlled treatment period; patients who maintained a \geq PASI 75 response at Week 33 and were originally randomized to active therapy in Period A were rerandomized (1:1) to receive adalimumab or placebo</p> | <u>Initial Dose</u> Adalimumab 80 mg | | | |
| | | <u>Period A - 16 weeks</u> Adalimumab 40 mg eow | 814 | 44.1 \pm 13.2 | 32.9 |
| | | Placebo | 398 | 45.4 \pm 13.4 | 35.4 |
| | | <u>Period B - 17 weeks</u> Adalimumab 40 mg eow | 606 | 43.9 \pm 13.2 | 30.7 |
| | | <u>Period C - 19 weeks</u> Adalimumab 40 mg eow | 250 | 44.3 \pm 13.0 | 29.6 |
| | | Placebo | 240 | 43.4 \pm 13.2 | 25.4 |
| M04-716 (Ps II) | Randomized, double-blind, double-dummy, multicenter, placebo- and active-controlled study in patients with moderate to severe plaque psoriasis (PASI \geq 10, BSA \geq 10%) who were candidates for systemic therapy or phototherapy and had inadequate response to topical therapy | Adalimumab 80 mg followed by 40 mg eow | 108 | 42.9 \pm 12.6 | 35.2 |
| | | Placebo | 53 | 40.7 \pm 11.4 | 34.0 |
| | | MTX capsules (7.5 to 25.0 mg) | 110 | 41.6 \pm 12.0 | 33.6 |
| | | Subcutaneous and oral 16 weeks | | | |
| M02-528 (Ps III) | Randomized, double-blind, placebo-controlled, multicenter, dose-ranging study in patients with moderate to severe plaque psoriasis (BSA \geq 5%) and inadequate response to topical therapy | adalimumab 80 mg followed by 40 mg eow | 45 | 45.8 \pm 11.6 | 28.9 |
| | | adalimumab 80 mg followed by 40 mg ew | 50 | 43.8 \pm 13.3 | 34.0 |
| | | Placebo Subcutaneous 12 weeks | 52 | 43.3 \pm 13.1 | 34.6 |

| Study # | Trial Design | Dosage, Route of Administration and Duration | Study Subjects (n) | Mean Age (Range) | Gender (% Female) |
|-----------------|---|---|--------------------|------------------|-------------------|
| M13-674 (Ps IV) | <p><u>Period A:</u> Double-blind, placebo-controlled treatment period during which patients with moderate to severe nail psoriasis (PGA and PGA-F of at least moderate disease severity; a target-fingernail mNAPSI ≥ 8 together with either BSA $\geq 10\%$ or a total mNAPSI score of ≥ 20 with $\geq 5\%$ BSA involvement) were randomized in a 1:1 ratio to receive adalimumab or placebo</p> <p><u>Period B:</u> Open-label treatment period; all patients received adalimumab</p> | <p><u>Period A – 26 weeks</u> adalimumab 80 mg followed by 40 mg eow Placebo</p> <p><u>Period B – 26 weeks</u> adalimumab 40 mg eow Subcutaneous 52 weeks</p> | 217 | 46.7 \pm 12.0 | 15.7 |

Definition(s): ew = every week; eow = every other week; MTX = methotrexate; PASI = Psoriasis Area and Severity Index; BSA = body surface area; PGA = Physician's Global Assessment; PGA-F Physician's Global Assessment of Fingernail Psoriasis; mNAPSI = Modified Nail Psoriasis Severity Index

Across all treatment groups of Study M03-656, the mean baseline Psoriasis Area and Severity Index (PASI) score was 18.9 and the baseline physician's global assessment (PGA) score ranged from "moderate" (52.6%) to "severe" (41.3%) to "very severe" (6.1%).

Across all treatment groups of Study M04-716, the mean baseline PASI score was 19.7 and the baseline PGA score ranged from "mild" (0.4%) to "moderate" (47.8%) to "severe" (45.6%) to "very severe" (6.3%).

Patients participating in all Phase 2 and Phase 3 psoriasis studies were eligible to enrol into an open-label extension trial, where adalimumab was given for at least an additional 108 weeks. 1,468 patients received at least one dose of adalimumab during the open-label trial. 1,018/1,468 (69%) patients received adalimumab for a minimum of 108 weeks. Patients from Study M03-656 who enrolled into the open-label trial may have received up to 160 weeks of continuous adalimumab exposure in the first portion of the extension. 183/233 (79%) eligible patients from Study M03-656 completed 160 weeks from the first dose of adalimumab in M03-656 to the end of the first portion of the extension trial.

Study Results

Clinical Response

In Studies M03-656, M04-716 and M02-528, the primary endpoint was the proportion of patients who achieved a reduction in PASI score of at least 75% (PASI 75) from baseline at Week 16 for Studies M03-656 and M04-716 and Week 12 for Study M02-528. Other evaluated outcomes in Studies M03-656, M04-716 and M02-528 included the PGA and other PASI measures.

Study M03-656 had an additional primary endpoint of loss of adequate response after Week 33 and on or before Week 52. Loss of adequate response is defined as a PASI score after Week

33 and on or before Week 52 that resulted in a < PASI 50 response relative to baseline with a minimum of a 6-point increase in PASI score relative to Week 33.

In Study M03-656, response to adalimumab was rapid, with significantly greater improvements compared to placebo in mean percentage PASI, PASI 75/90 response rates, and PGA clear or minimal scores by Week 4, the first study visit (all $p < 0.001$ vs. placebo).

In Studies M03-656 and M04-716, more patients randomized to adalimumab than to placebo achieved at least a 75% reduction from baseline of PASI score at Week 16 (see [Table 56](#) and [Table 57](#)). Other relevant clinical parameters, including PASI 90, PASI 100 (corresponding to a complete clearance of psoriasis skin signs) and PGA of “clear or minimal,” were also improved over placebo.

In Study M04-716, superior results were achieved for PASI 75, PASI 90, PASI 100 and PGA of “clear or minimal” in patients randomized to the adalimumab treatment group versus those randomized to receive MTX.

Table 56 Psoriasis Study M03-656 Efficacy Results at Week 16 (Percent of Patients)

| Response | Placebo N = 398 | Adalimumab 40 mg eow N = 814 |
|--------------------|--------------------|---------------------------------|
| ≥ PASI 75 | 6.5% | 70.9% ^a |
| ≥ PASI 90 | 1.8% | 45.0% ^a |
| PASI 100 | 0.8% | 20.0% ^a |
| PGA: Clear/minimal | 4.3% | 62.2% ^a |

^a $p < 0.001$ for adalimumab versus placebo

Definition(s): eow = every other week; PASI = Psoriasis Area Severity index; PGA = physician’s global assessment

Table 57 Psoriasis Study M04-716 Efficacy Results at Week 16 (Percent of Patients)

| Response | Placebo N = 53 | MTX N = 110 | Adalimumab 40 mg eow N = 108 |
|--------------------|-------------------|----------------|------------------------------------|
| ≥ PASI 75 | 18.9% | 35.5% | 79.6% ^{a,b} |
| ≥ PASI 90 | 11.3% | 13.6% | 51.9% ^{a,b} |
| PASI 100 | 1.9% | 7.3% | 16.7% ^{c,d} |
| PGA: Clear/minimal | 11.3% | 30.0% | 73.1% ^{a,b} |

^a $p < 0.001$ for adalimumab versus placebo

^b $p < 0.001$ for adalimumab versus methotrexate

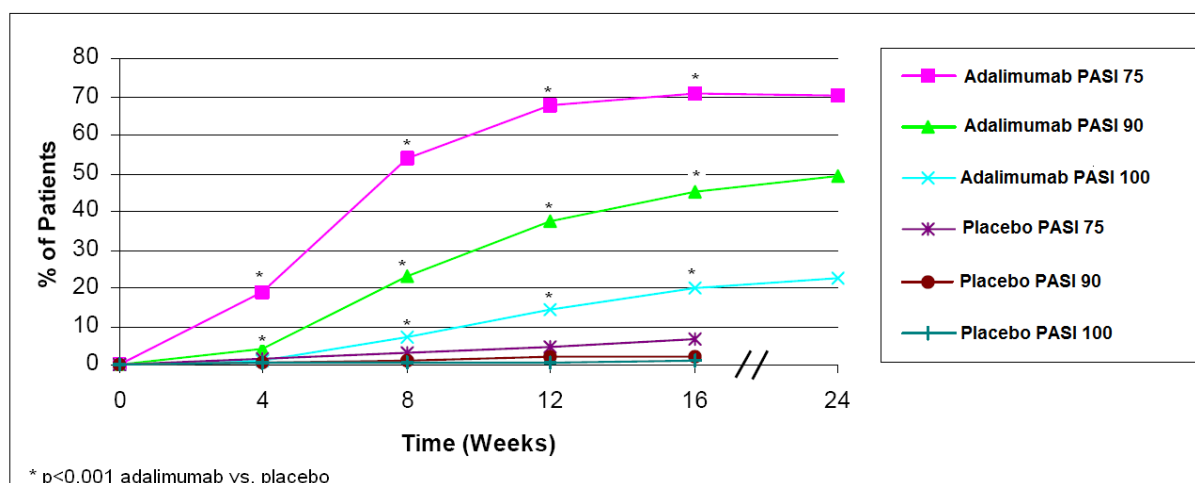
^c $p < 0.01$ for adalimumab versus placebo

^d $p < 0.05$ for adalimumab versus methotrexate

Definition(s): MTX = methotrexate; eow = every other week; PASI = Psoriasis Area Severity index; PGA = physician’s global assessment

PASI 75, PASI 90 and PASI 100 Responses from Week 0 to Week 24 for Study M03-656 are presented in [Figure 5](#).

Figure 5. Psoriasis Study M03-656 Response Rate from Week 0 to Week 24



Results from Study M02-528 supported the efficacy demonstrated in Studies M03-656 and M04-716.

In Study M03-656, patients who were PASI 75 responders and were re-randomized to continue adalimumab therapy at Week 33 were less likely to experience a loss of adequate response on or before Week 52 than the PASI 75 responders who were re-randomized to placebo at Week 33 (4.9% versus 28.4%, $p < 0.001$).

A total of 233 PASI 75 responders at Week 16 and Week 33 received continuous adalimumab therapy for 52 weeks in Psoriasis Study M03-656, and continued adalimumab in the open-label extension (OLE) trial. The proportion of patients with full skin clearance (PASI 100) was generally maintained through Week 108 [31.8% at OLE entry ($n = 74/233$); 30.1% at Week 108 ($n = 69/229$ (total of 160 weeks))].

A total of 94 patients were randomized to adalimumab therapy in Psoriasis Study M04-716, and continued adalimumab in the open label extension trial. The proportion of patients with PASI 75 after an additional 108 weeks of open-label therapy was 58.1% ($n = 54/93$) (total of 124 weeks).

A total of 347 stable responders participated in a withdrawal and retreatment evaluation in an open-label extension study. Median time to relapse (decline to PGA “moderate” or worse) was approximately 5 months [95% C.I. (127, 146 days)]. None of these patients experienced rebound during the withdrawal period. A total of 76.5% (218/285) of patients who entered the retreatment period had a response of PGA “clear” or “minimal” after 16 weeks of retreatment, 69.1% (123/178) for patients who relapsed and 88.8% (95/107) for patients who did not relapse during the withdrawal period.

In the open-label extension study, 349/1,256 (27.8%) patients dose escalated from 40 mg every other week to 40 mg weekly due to a PASI response below 50% and were evaluated 12 weeks after dose escalation, and 93/349 (26.6%) patients achieved PASI 75 response.

There were no clinical trials conducted to evaluate the efficacy and safety of adalimumab in psoriatic arthritis subjects with both active arthritis and moderate to severe psoriasis.

Study M13-674 evaluated the proportion of patients who achieved “clear” or “minimal” nail psoriasis with at least a 2-grade improvement on the 5-point Physician’s Global Assessment of Fingernail Psoriasis (PGA-F) scale and at least a 75% improvement in Modified Nail Psoriasis Severity Index (mNAPSI 75) at Week 26. At Week 26, a statistically significantly higher

proportion of patients in the adalimumab group achieved a PGA-F and mNAPSI 75 response compared with placebo (see [Table 58](#)).

Table 58. Nail Psoriasis Study M13-674 Efficacy Results at 26 Weeks

| Response | Placebo N = 108 | Adalimumab 40 mg eow N = 109 |
|--|----------------------------|---|
| PGA-F clear/minimal and \geq 2-grade improvement | 6.9% | 48.9% ^{a,b} |
| \geq mNAPSI 75 | 3.4% | 46.6% ^{a,b} |

^a $p < 0.001$ for adalimumab versus placebo

^b Across all the strata, P value was calculated according to the Cochran-Mantel-Haenszel test adjusted for strata. If zero frequency occurred, strata were dropped and P value was calculated based on Chi-square test (or adjusted Chi-square test based on Campbell (2007) if expected count < 5 in any cell).

Definition(s): PGA-F Physician's Global Assessment of Fingernail Psoriasis; mNAPSI = Modified Nail Psoriasis Severity Index

Quality of Life

Patient Reported Outcomes (PRO) were evaluated by several measures. Quality of Life was assessed using the disease-specific Dermatology Life Quality Index (DLQI) in Study M03-656 and Study M04-716.

In Study M03-656, patients receiving adalimumab demonstrated clinically meaningful improvement in the DLQI total score, disease severity, pain, and pruritus compared to the placebo group at both Weeks 4 and 16. The DLQI result was maintained at Week 52.

In Study M04-716, patients receiving adalimumab demonstrated clinically meaningful improvement in the DLQI total score, disease severity, and pruritus compared to the placebo and MTX groups at Week 16, and clinically meaningful improvement in pain compared to the placebo group at Week 16.

The Short Form Health Survey (SF-36) was used to assess general health-related quality of life in Study M03-656. The adalimumab-treated patients had significantly greater improvement in the SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores.

17.1.8 Uveitis

Study Demographics and Trial Design

The safety and efficacy of adalimumab were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis (also known as "non-infectious uveitis affecting the posterior segment"), excluding patients with isolated anterior uveitis, in two randomized, double-masked, placebo-controlled studies (M10-877 and M10-880) and an ongoing open-label extension study (M11-327). Patients received placebo or adalimumab at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. Concomitant stable doses of non-biologic immunosuppressants were permitted.

[Table 59](#) summarizes the controlled and open-label extension clinical trials in patients with uveitis.

Table 59 Summary of Clinical Trials Supporting Safety and Efficacy in Patients with Uveitis

| Study # | Trial Design | Dosage, Route of Administration and Duration | Study Subjects (n) | Mean Age (Range) | Gender (% Female) |
|----------------------|---|--|--------------------|-------------------------|-------------------|
| M10-877 (VISUAL I) | Randomized, double-masked, placebo-controlled, multicenter study | adalimumab 80 mg loading dose, followed by 40 mg given eow starting at Week 1 | 110 | 42.7 ± 15.6 (18 to 81) | 53.6 |
| | | Placebo Subcutaneous Up to 80 weeks | 107 | 42.6 ± 14.2 (18 to 79) | 60.7 |
| M10-880 (VISUAL II) | Randomized, double-masked, placebo-controlled, multicentre study | adalimumab 80 mg loading dose, followed by 40 mg given eow SC starting at Week 1 | | 42.9 ± 12.9 (18 to 75) | 57.4 |
| | | Placebo Subcutaneous Up to 80 weeks | | 42.2 ± 13.98 (20 to 29) | 64.9 |
| M11-327 (VISUAL III) | Open-label extension of controlled Studies M10-877 and M10-880 for patients who had either discontinued from the lead-in studies for having met “treatment failure” criteria (active uveitis subgroup) or had completed the lead-in studies without treatment failure (inactive uveitis subgroup) | Adalimumab 40 mg eow Subcutaneous At least 78 weeks | 424 | 43.4 ± 14.1 (19 to 81) | 58.7 |

Definition(s): eow = every other week; SC = subcutaneous

Description of Clinical Studies

The primary efficacy endpoint in both controlled studies was “time to treatment failure”. Treatment failure was defined by a multi-component measurement assessing the loss of disease control based on inflammatory chorioretinal and/or inflammatory retinal vascular lesions, anterior chamber (AC) cell grade, vitreous haze (VH) grade and best corrected visual acuity (BCVA).

Study M10-877 evaluated 217 patients with active uveitis despite treatment with corticosteroids (oral prednisone at a dose of 10 to 60 mg/day). All patients received a standardized dose of prednisone 60 mg/day at study entry followed by a mandatory taper schedule, with complete corticosteroid discontinuation by Week 15.

Study M10-880 evaluated 226 patients with inactive uveitis requiring chronic corticosteroid treatment (oral prednisone 10 to 35 mg/day) at baseline to control their disease. Patients subsequently underwent a mandatory taper schedule, with complete corticosteroid discontinuation by Week 19.

Study M11-327 evaluated the long-term safety and efficacy of adalimumab 40 mg every other week in the treatment of uveitis, during which corticosteroid/immunosuppressant treatments could be initiated, maintained, escalated, tapered, or discontinued as needed.

Study Results

Clinical Responses

Results from both studies demonstrated statistically significant reduction of the risk of treatment failure over the course of the study in patients treated with adalimumab versus patients receiving placebo (Table 60, Figure 6, Figure 7).

Table 60 Time to Treatment Failure in Uveitis Studies

| Analysis Treatment | N | Failure N (%) | Median Time to Failure (Weeks/Months) | HR ^a | CI 95% for HR ^a | P value ^b |
|--|-----|---------------|---------------------------------------|-------------------|----------------------------|----------------------|
| Time to Treatment Failure At or After Week 6 in Study M10-877 | | | | | | |
| Primary analysis (ITT) | | | | | | |
| Placebo | 107 | 84 (78.5) | 13.0/3.0 | - | - | - |
| Adalimumab | 110 | 60 (54.5) | 24.4/5.6 | 0.50 ^b | 0.36, 0.70 ^b | < 0.001 |
| Time to Treatment Failure At or After Week 2 in Study M10-880 | | | | | | |
| Primary analysis (ITT) | | | | | | |
| Placebo | 111 | 61 (55.0) | 36.1/8.3 | - | - | - |
| Adalimumab | 115 | 45 (39.1) | NE ^c | 0.57 ^b | 0.39, 0.84 ^b | 0.004 |

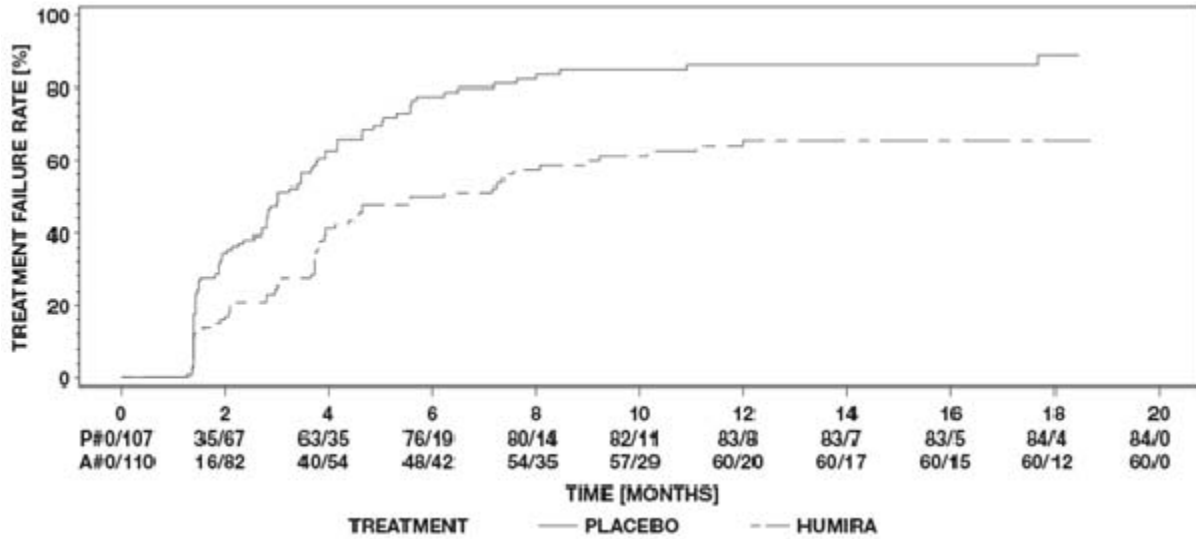
Note: Treatment failure at or after Week 6 (Study M10-877), or at or after Week 2 (Study M10-880), was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

^a HR of adalimumab vs placebo from proportional hazards regression with treatment as factor.

^b 2-sided P Value from log rank test.

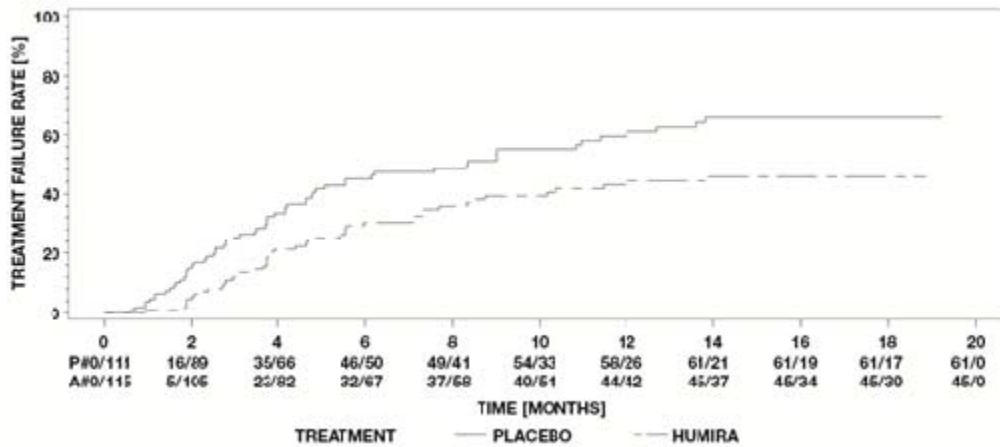
^c NE = not estimable. Fewer than half of at-risk subjects had an event.

Figure 6 Kaplan-Meier Curves Summarizing Time to Treatment Failure on-or-after Week 6 (Study M10-877)



Note: P# = Placebo (Number of Events/Number at Risk); A# = adalimumab (Number of Events/Number at Risk)

Figure 7 Kaplan-Meier Curves Summarizing Time to Treatment Failure on-or-after Week 2 (Study M10-880)



Note: P# = Placebo (Number of Events/Number at Risk); A# = adalimumab (Number of Events/Number at Risk)

In both studies, all components of the primary endpoint contributed cumulatively to the overall difference between adalimumab and placebo groups.

17.2 Pediatric

17.2.1 Polyarticular Juvenile Idiopathic Arthritis

Study Demographics and Trial Design

The safety and efficacy of adalimumab was assessed in two studies (Studies DE038 and M10-444) in children with active polyarticular or polyarticular course juvenile idiopathic arthritis (JIA), who had a variety of JIA onset types (most frequently rheumatoid-factor negative or positive polyarthritis and extended oligoarthritis).

Table 61 summarizes the clinical trials that were done in patients with polyarticular JIA.

Table 61 Summary of Clinical Trial Evaluating Safety and Efficacy in Patients with Polyarticular Juvenile Idiopathic Arthritis

| Study # | Trial Design | Dosage, Route of Administration and Duration | Study Subjects (n) | Mean Age (Range) (Years) | Gender (% Female) |
|------------------|---|--|--------------------|---------------------------|-------------------|
| DE038 (JIA I) | Multicenter, double-blind, randomized, placebo-controlled, open-label extension | <u>OL LI Phase</u> 24 mg adalimumab/m ² BSA (up to a maximum of 40 mg total body dose) subcutaneous eow | 171 | 11.3 ± 3.53 (4 to 17) | 78.9% |
| | | <u>DB Phase</u> 24 mg adalimumab/m ² BSA (up to a maximum of 40 mg total body dose) subcutaneous eow or Placebo subcutaneous eow | 133 | 11.6 ± 3.61 (4 to 17) | 77.4% |
| | | <u>OLE BSA Phase</u> 24 mg adalimumab/m ² BSA (up to a maximum of 40 mg total body dose) subcutaneous eow | 128 | 12.0 ± 3.59 (4 to 18) | 76.6% |
| | | <u>OLE FD Phase</u> 20 mg adalimumab subcutaneous eow, < 30 kg body weight or 40 mg adalimumab subcutaneous eow, ≥ 30 kg body weight | 106 | 13.7 ± 3.82 (6 to 20) | 73.6% |
| M10-444 (JIA II) | Multicenter, open-label | 24 mg adalimumab/m ² BSA (up to a maximum of 20 mg total body dose) subcutaneous eow | 32 | 3.04 ± 0.723 (2.0 to 4.6) | 87.5% |

Definition(s): BSA = body surface area; DB = double blind; eow = every other week; OL BSA = open-label body surface area; OL FD = open-label fixed dose; OL LI = open-label lead in; SC = subcutaneous.

Description of Clinical Studies

Study DE038

The safety and efficacy of adalimumab were assessed in a multicentre, randomized, double-blind, parallel-group study in 171 pediatric patients (4 to 17 years old at the time of enrollment) with moderate or severe JIA. In the open-label lead in phase (OL LI) patients were stratified into two groups, MTX-treated or non-MTX-treated. Patients who were in the non-MTX stratum were either naive to or had been withdrawn from MTX at least two weeks prior to study drug administration. Patients remained on stable doses of NSAIDs and or prednisone (≤ 0.2 mg/kg/day or 10 mg/day maximum). In the OL LI phase all patients received 24 mg/m² up to a maximum of 40 mg adalimumab every other week for 16 weeks. The distribution of patients by age and minimum, median and maximum dose received during the OL LI phase is presented in [Table 62](#).

Table 62 Distribution of Patients by Age and adalimumab dose received during the OL LI phase

| Age Group | Number of patients at Baseline n (%) | Minimum, median and maximum dose |
|----------------|--------------------------------------|----------------------------------|
| 4 to 7 years | 31 (18.1) | 10, 20 and 25 mg |
| 8 to 12 years | 71 (41.5) | 20, 25 and 40 mg |
| 13 to 17 years | 69 (40.4) | 25, 40 and 40 mg |

Definition(s): OL LI = open-label lead in

Patients demonstrating a Pediatric ACR 30 response at Week 16 were eligible to be randomized into the double-blind phase and received either adalimumab 24 mg/m² up to a maximum of 40 mg, or placebo every other week for an additional 32 weeks or until disease flare. Disease flare criteria were defined as a worsening of $\geq 30\%$ from baseline in ≥ 3 of 6 Pediatric ACR core criteria, ≥ 2 active joints, and improvement of $> 30\%$ in no more than 1 of the 6 criteria.

After 32 weeks or at disease flare, patients were eligible to enroll into the open label extension phase.

The primary efficacy variable was the proportion of patients in the non-MTX stratum who experienced disease flare in the double-blind phase. Key secondary endpoints were analysis and comparison of disease flare at Week 48 including the proportion of patients with disease flare in those treated with MTX, time to onset (from double blind Baseline) of flare for patients in the non-MTX stratum, and time to onset (from double blind Baseline) of flare for patients treated with MTX. Subjects were clinically assessed at baseline, and for clinical response to adalimumab at Weeks 2, 4 and then every 4 weeks up to Week 48 or at early termination and throughout the OLE phases.

Study M10-444

The safety and efficacy of adalimumab was assessed in an open-label, multicenter study in 32 children (2 to < 4 years old or aged 4 and above weighing < 15 kg) with moderately to severely active polyarticular JIA. The primary objective of the study was the evaluation of safety. The patients received 24 mg/m² body surface area (BSA) of adalimumab up to a maximum of 20 mg every other week as a single dose via SC injection for at least 24 weeks up to a maximum of 120 weeks duration. During the study, most subjects used concomitant MTX, with fewer reporting use of corticosteroids or NSAIDs.

Study Results

Table 63 Major Efficacy Results in the JIA Study (DE038)

| Stratum | MTX | | Without MTX | |
|---|------------------------|---------------------|------------------------|----------------------------|
| Phase | | | | |
| OL-LI 16 weeks | | | | |
| Ped ACR 30 response* (n/N) | 94.1% (80/85) N=85* | | 74.4% (64/86) N=86* | |
| Double Blind | Adalimumab (n = 38) | Placebo (n = 37) | Adalimumab (n = 30) | Placebo (n = 28) |
| Disease flares at the end of 32 weeks (n/N) | 36.8% (14/38) | 64.9% (24/37) | 43.3% (13/30) | 71.4% (20/28) ^a |
| Median time to disease flare | >32 weeks | 20 weeks | >32 weeks | 14 weeks |

^a p = 0.031

* N and PedACR30 response rates are from the Open-Label Lead-In phase prior to the randomization to the Double-Blind phase.

Definition(s): MTX = methotrexate; OL-LI = open-label lead in; Ped ACR = pediatric American College of Rheumatology

Twelve patients were treated for 6 years or longer.

The percentage of patients achieving PedACR30 responses were higher (94% vs. 74%) and, fewer patients developed antibodies (5.9% vs. 25.6%) when treated with the combination of adalimumab and MTX compared to adalimumab monotherapy. Therefore, adalimumab is recommended for use in combination with MTX, and for use as monotherapy only in patients for whom MTX use is not appropriate.

17.2.2 Pediatric Crohn's Disease

Study Demographics and Trial Design

The safety and efficacy of adalimumab were assessed in a multicenter, randomized, double-blind clinical study (M06-806) in 192 pediatric patients, 6 to 17 years of age (mean age 13.6 years), with moderately to severely active Crohn's disease defined as Pediatric Crohn's Disease Activity Index (PCDAI) score > 30 who have had an inadequate response to conventional therapy or had lost response to infliximab (approximately 44%). Of the 192 pediatric patients, 188 were randomized during the double-blind period (median baseline PCDAI value of 40, range 25.0 to 62.5).

Patients received open-label induction therapy at a dose based on their Baseline body weight. At Week 4, 188 patients were randomized 1:1 based on their body weight to the DB Maintenance period. The majority of patients were male (55.9%), Caucasian (88.3%), ≥ 13 years of age (64.9%) and weighed ≥ 40 kg (64.4%). The greatest proportion of patients had Crohn's disease of the colon (81.9%) and or ileum (77.1%). There were no statistically significant differences observed between the dose regimen groups in Baseline characteristics. 102 patients were 13 to 17 years of age weighing ≥ 40 kg (median PCDAI value of 40.0, range 25.0 to 62.5).

Study Results

Study M06-806

Clinical Response

Clinical remission (defined as PCDAI score ≤ 10) and clinical response (defined as reduction in PCDAI score of at least 15 points from Baseline) rates for the indicated pediatric patient population with Crohn's disease are presented in [Table 64](#).

Table 64 Rates of Clinical Remission and Response During the Double-Blind Maintenance Phase

| Response | | High-Dose 40 mg eow N = 52 | Low-Dose 20 mg eow N = 50 |
|----------|--------------------|----------------------------------|---------------------------------|
| Week 26 | Clinical remission | 40.4% | 36.0% |
| | Clinical response | 63.5% | 54.0% |

Definition(s): eow = every other week

Of the 52 patients who received High-Dose, the rates of clinical remission and clinical response at Week 52 were 32.7 and 42.3%, respectively. Of the 50 patients who received Low-Dose, the rates of clinical remission and clinical response at Week 52 were 30.0 and 32.0%, respectively.

The rate of clinical remission was higher among all adalimumab patients who had no prior exposure to infliximab compared to those with prior exposure to infliximab (53.8% versus 22.0% and 38.5% versus 24.0% at Weeks 26 and 52, respectively).

At Week 26, a higher proportion of patients achieved PCDAI clinical remission if they were naïve to infliximab therapy [High-Dose 63.0% (17/27) and Low-Dose 44.0% (11/25)], compared to patients who had previously failed infliximab therapy [High-Dose 16.0% (4/25) and Low-Dose 28.0% (7/25)]. At Week 52, a higher proportion of patients achieved PCDAI clinical remission if they were naïve to infliximab therapy [High-Dose 44.4% (12/27) and Low-Dose 32.0% (8/25)], compared to patients who had previously failed infliximab therapy [High-Dose 20.0% (5/25) and Low-Dose 28.0% (7/25)].

The median baseline PCDAI value for patients naïve to infliximab was 37.5 (range 25.0 to 50.0) and 37.5 (range 30.0 to 55.0) for High-Dose and Low-Dose, respectively. The median baseline PCDAI value for patients who had previously failed infliximab therapy was 40.0 (range 32.5 to 62.5) and 40.0 (range 32.5 to 60.0) for High-Dose and Low-Dose, respectively.

Of the patients who had fistulas at Baseline, 55.6% (5/9) and 53.8% (7/13) in the High-Dose and Low-Dose groups, respectively, achieved fistula healing (defined as closure of all fistulas that were draining at Baseline for at least 2 consecutive post Baseline visits) at Week 26, and 55.6% (5/9) and 23.1% (3/13), respectively, achieved fistula healing at Week 52.

The rates of early discontinuation during the double-blind period were 17.3% (9/52) in the High-Dose group and 22.0% (11/50) in the Low-Dose group.

17.2.3 Adolescent Hidradenitis Suppurativa

No clinical trials were conducted in adolescent patients with hidradenitis suppurativa. Efficacy of adalimumab for the treatment of adolescent patients with hidradenitis suppurativa (12 to 17 years of age weighing ≥ 30 kg) is predicted using pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulations based on demonstrated efficacy and exposure-response relationship in adult hidradenitis suppurativa patients (see **CLINICAL TRIALS [17.1.6]**).

The disease course, pathophysiology and drug effects in adolescents are assumed to be similar to adults at the same exposure levels. Safety of the recommended adalimumab dose in adolescent hidradenitis suppurativa population is based on cross-indication safety profile of adalimumab in both adults and pediatric patients at similar or higher exposures.

17.2.4 Pediatric Uveitis

Study Demographics and Trial Design

The safety and efficacy of adalimumab were assessed in a randomized, double-masked, controlled study of 90 pediatric patients from 2 to < 18 years of age with active JIA-associated non-infectious anterior uveitis who were refractory to at least 12 weeks of MTX treatment. Participants were randomized applying a ratio of 2:1 (adalimumab:placebo) stratified by centre. Patients received either placebo or 20 mg adalimumab (if < 30 kg) or 40 mg adalimumab (if ≥ 30 kg) every other week in combination with their baseline dose of MTX for up to 18 months. Concomitant stable dosages of systemic (≤ 0.2 mg/kg/day of prednisolone equivalent) and topical corticosteroids (maximum 6 drops/day) were permitted at study entry followed by a mandatory reduction in topical corticosteroids (maximum 2 drops/day) within 3 months.

[Table 65](#) summarizes the controlled clinical trial done in pediatric patients with uveitis.

Table 65. Summary of Controlled Clinical Trial Supporting Safety and Efficacy in Pediatric Patients with Uveitis

| Study # | Trial Design | Dosage, Route of Administration and Duration | Study Subjects (n) | Mean Age (Range) | Gender (% Female) |
|----------|---|--|--------------------|---------------------------------|-------------------|
| SYCAMORE | Randomized, double-masked, placebo-controlled | adalimumab fixed dose of 20 mg (if BW < 30 kg at Baseline) or 40 mg (if BW ≥ 30 kg at Baseline) | 60 | 9.07 \pm 3.94 (3.04 to 17.97) | 78.3 |
| | | Placebo | 30 | 8.56 \pm 3.79 (2.57 to 16.9) | 76.7 |
| | | Subcutaneous Every 2 weeks for up to 18 months | | | |

Definition(s): BW = body weight

Description of Clinical Studies

The primary efficacy endpoint was “time to treatment failure”. The criteria determining treatment failure were worsening or sustained non-improvement in ocular inflammation, partial improvement with development of sustained ocular co-morbidities or worsening of ocular co-morbidities, non-permitted use of concomitant medications, and suspension of treatment for an extended period of time.

Study Results

Clinical Response

Adalimumab delayed the time to treatment failure, as compared to placebo (See Figure 8 and Table 66). These results are based on the 2nd interim analysis, which was performed when 90 patients out of a total planned sample size of 114 patients had been randomized in the study.

Table 66. Results of Time to Treatment Failure Analysis in the Pediatric Uveitis Study

| Treatment/ Reason for Failure | N | Failure n (%) | Median Time to Failure (Weeks) ^a | HR ^b | 99.9% CI for HR ^{b,c} | P value ^{c,d} |
|--|----|---------------|---|-----------------|--------------------------------|------------------------|
| Placebo | 30 | 18 (60.0) | 24.1 | - | - | - |
| Anterior segment inflammation or ocular co-morbidity | | 7 (23.3) | | | | |
| Use of prohibited concomitant medication | | 10 (33.3) | | | | |
| Suspension of study treatment | | 1 (3.3) | | | | |
| Adalimumab | 60 | 16 (26.7) | NE ^f | 0.25 | 0.08, 0.79 | < 0.0001 |
| Anterior segment inflammation or ocular co-morbidity | | 2 (3.3) | | | | |
| Use of prohibited concomitant medication | | 11 (18.3) | | | | |
| Suspension of study treatment | | 4 (6.7) | | | | |

^a Estimated based on Kaplan-Meier curve.

^b HR of adalimumab versus placebo from proportional hazards regression with treatment as factor.

^c Significance level of 0.001 was used at the interim analysis based on the Peto-Haybittle stopping rule.

^d Derived from log rank test.

^e One adalimumab patient had two reasons for treatment failure (use of prohibited concomitant medication and suspension of study treatment).

^f NE = not estimable. Fewer than half of at-risk subjects had an event.

Definition(s): CI = Confidence Interval; HR = Hazard Ratio

an ELISA and to detect MAHA formation with two different ELISA techniques. All animals were sacrificed and subjected to gross examination upon termination of the study. Spleen and skin were evaluated histopathologically.

The general deportment of the mice and the body weight gains were not affected by treatment with adalimumab. One male at 1.6 mg/kg died on Day 13 during blood sampling under halothane anesthesia. The death of this animal was considered to be associated with the halothane anesthesia and not associated with the adalimumab treatment. Local hair loss in the nasolabial area associated with loss of tactile hairs was observed in all females at 1.6 mg/kg and four out of five females in the control group from Week 5 onwards. The results indicate that the hair loss is not associated with adalimumab treatment since the same effect also was observed in the control mice.

The serum concentration curve of adalimumab was plotted for one mouse from each group. In the control and 1.6 mg/kg groups, the adalimumab serum concentration was always less than 0.6 mcg/mL, whereas at 16 mg/kg group, 70 mcg/mL was found at Week 3. No adalimumab was detected from Week 5 onwards at this dose. At 786 mg/kg group, a concentration as high as 484 mcg/mL was found at Week 3 and a measurable concentration of adalimumab was found up to nine weeks post injection.

The time course of MAHA development also was measured in one mouse from each group. MAHAs were not detected in the control mouse or any pre-treatment sample. Using a double sandwich (double antigen) MAHA assay (called MAHA-1 assay in the report) sensitive to inhibition by adalimumab in the blood, MAHAs were detected as early as Week 5 for the mouse treated at 1.6 mg/kg and not detected until Week 11 for the mouse treated at 16 mg/kg, whereas MAHAs were not detected at any time point for the mouse treated at 786 mg/kg, which was attributed to the assay interference by the high concentrations of circulating adalimumab. Using a direct capture (sandwich) MAHA assay (called MAHA-2 assay in the report) that is less sensitive to adalimumab interference, MAHAs were detected from Week 5 onwards in mice at 1.6 mg/kg and 16 mg/kg and at Weeks 9 and 13 in the 786 mg/kg mouse. Once the kinetics and titers were determined from the sample mouse of each group, MAHAs in all mice treated with adalimumab were analyzed at a dilution of 1:1000 at Week 5 for the 1.6 mg/kg and 16 mg/kg mice, and at Week 13 for the 786 mg/kg mice by the direct capture MAHA assay. MAHAs were detected in all samples, indicating that all the adalimumab-treated mice were MAHA positive after a single intravenous injection.

In the rat single-dose study, a single dosage of adalimumab (898 mg/kg, drug substance batch AF601-Ex pool) or vehicle control (PBS) was administered via a tail vein (5/sex/group). The animals were examined for clinical signs for 14 days after drug administration. Necropsy was performed 14 days after treatment.

At the highest technically feasible dosage of 898 mg/kg adalimumab based on a 10 mL/kg injection volume and the highest available drug concentration, no deaths occurred. Drug-related clinical signs were not observed. Body weight gains of the drug-treated rats were comparable to those of the control rats. Necropsy showed slightly to moderately enlarged spleens in three males at 898 mg/kg, and slightly enlarged spleens in three males in the control group. Histopathology of the enlarged spleens revealed moderate to marked extramedullary hematopoiesis. These changes were not attributed to the drug treatment because they were observed in the control group as well as in the treatment group.

In summary, adalimumab is well tolerated at the highest technically feasible dose and the minimal lethal dose after a single intravenous injection is greater than 898 mg/kg in mice and rats. Adalimumab is immunogenic in mice after a single intravenous dose.

Long-Term Toxicity – Multiple-Dose Studies

Mouse (Four-Week Study)

In a four-week mouse study, the mice were randomly distributed into three study groups. The highest dose in this study provided 16 times the maximum dosage of 10 mg/kg used in early clinical studies.

The mice were intravenously administered either vehicle control (PBS) or adalimumab (drug substance batch AFP603) once per week on days 1, 8, 15, 22, and 29. The main study group was terminated on Day 30 and the recovery study group was allowed to recover for four weeks without further treatment after the last dose. The mice were observed for drug-related clinical signs at least once daily. Body weight and food consumption was recorded once weekly. Blood samples (0.3 mL) in the main and recovery study groups were collected from the retro-orbital venous plexus under light ether anesthesia on Days 30 and 57 (recovery group only) from mice chosen for hematology, clinical biochemistry and immunogenicity analyses.

There was no clinical sign of toxicity or behavioral changes related to drug treatment. Body weight and body weight gain of drug-treated animals remained in the same range as controls over the treatment and recovery periods.

The results of the toxicokinetic evaluation, using adalimumab level values from pooled serum, revealed that weekly iv administrations of 32, 70.9 and 157.2 mg/kg of adalimumab to mice for four weeks resulted in an increase of serum C_{max} and AUC values (C_{max}: 1193, 1528, 4231 mcg/mL in males, 794, 2069, 5028 mcg/mL in females; AUC: 66782, 104612, 190342 mcg•h/mL in males, 81598, 120693, 240366 mcg•h/mL in females). A slightly lower terminal half-life was observed for male mice than for female mice (97 to 112 hours versus 134 to 259 hours). The AUC values increased in a slightly less than proportional manner and were somewhat higher in female mice. There was, however a high degree of variability in the data.

Significant formation of MAHAs was detected in male and female mice in all drug-treated groups starting on the 8th day after the first administration. The level of MAHAs increased with subsequent doses. Significant differences were observed between 32.0 mg/kg and 70.9 mg/kg dosages ($p < 0.01$) and the 32.0 mg/kg and 157.2 mg/kg dosages ($p < 0.01$), but not between the 70.9 mg/kg and 157.2 mg/kg dosages ($p > 0.05$). This indicates that the MAHAs are detected at all dose levels. Whether the differences between dose levels are due to assay interference or true differences in immunogenicity can not be determined.

Monkey (Four-Week Study)

A four-week study was performed to investigate the potential toxicity of adalimumab in cynomolgus monkeys. A total of 32 monkeys (16 males and 16 females) were distributed randomly into four dosage groups, and were administered either the vehicle control (PBS), or adalimumab at 32, 70.9, or 157.2 mg/kg (drug substance batch AFP603) via intravenous injection (vena saphena magna of the right or left hind leg). The injections were given once per week on days 1, 8, 15, 22, and 29 for a total of five doses.

The toxicokinetic results showed a dose-proportional increase of serum maximum concentration (C_{max}) of adalimumab and serum AUC. The central volume of distribution ($V_c = \text{dose} / C(0)$) was 39.7 ± 7.9 mL/kg (mean \pm standard deviation). The AUCs corresponding to single-dose amounts of 32, 70.9, and 157.2 mg/kg, were 201317 ± 88835 , 359667 ± 127283 and 808900 ± 200581 mcg•h/mL, respectively. The terminal half-life was 13.5 ± 4.6 days and the clearance was 0.20 ± 0.07 mL/h/kg. No sex dependency of pharmacokinetic parameters and no influence of dose on total clearance were noted.

Immunohistochemistry data showed a minimal decrease of CD21+ B-cells in the spleen follicles of the male monkeys treated with 70.9 and 157.2 mg/kg.) A reduced cytoplasmic immunostaining of IgG and IgM was also observed in the germinal centers of the follicles in most treated monkeys at all doses. No such change was observed in the follicles in the lymph nodes. All these changes were very subtle and generally reversible. Therefore, these changes were considered to be the result of pharmacologically functional effects of adalimumab rather than toxicological effects. No deposits of immune-complexes were found in kidney, lung, liver, skin, spleen, thymus, lymph nodes, skeletal muscle, and heart.

Monkey (39-Week Study)

A 39-week study in cynomolgus monkeys was done to evaluate the potential toxicity and reversibility of any toxic effect of adalimumab. A total of 32 animals (16 males and 16 females) were randomly distributed into four groups, and were administered either vehicle control (PBS buffer) or adalimumab at 32, 82.9, or 214.8 mg/kg. The test article or control agent was administered by intravenous injection into a vena saphena magna, once per week for 39 weeks (total of 40 injections).

There were no significant differences in clinical signs of toxicity or behavior and food consumption over the treatment and recovery periods in the drug-treated groups as compared to the control animals. Body weights of the animals treated with 32 and 82.9 mg/kg were not affected as compared with the control animals. In the 214.8 mg/kg group, a slight, transient decrease in the body weight was observed in test Week 4, and completely recovered from test Week 6 onwards. The body weights of the female animals in this group were decreased slightly from test Week 2 onwards. The decreases were not statistically significant at $p \leq 0.01$ as compared with the control animals and were within the normal fluctuation of body weight.

The examination of immune complexes showed a reduced antigen expression of IgG and IgM in the follicular dendritic cells of the spleen in all drug-treated monkeys. Concomitantly, the follicular dendritic cells were reduced in number and the normally dense network was altered. In parallel, the IgG or IgM positive plasma cell count increased slightly in the spleen independently of the different compartments. These changes were considered to be the pharmacologically functional effects of adalimumab rather than toxicological effects.

Toxicokinetic results reported in Report No. MPF/EBB 9741 showed an increase of steady-state serum concentrations and AUC values. At dosages of 32, 82.9, and 214.8 mg/kg of adalimumab, the corresponding C_{max} (mean \pm standard deviation) at five minutes after the last administration were 2731 ± 467 , 6527 ± 2450 , 13563 ± 1740 mcg/mL and the corresponding serum AUCs were 304774 ± 74634 , 617368 ± 233959 , and 1299965 ± 228114 mcg·h/mL, respectively. The corresponding clearances were 0.11 ± 0.04 , 0.16 ± 0.07 , and 0.17 ± 0.03 mL/h/kg, respectively. The terminal half-life, evaluated from data obtained during the recovery phase of two male and two female monkeys, was 16.2 ± 3.4 days. No sex dependency of pharmacokinetic parameters and no influence of dose on the clearance were noted.

The distribution of adalimumab in the vascular compartment was broad in the lungs, liver, and skin at 214.8 mg/kg. Cartilage staining in the bronchi with anti-adalimumab antibodies was observed in several treated monkeys at 32 mg/kg onwards. In the synovial membrane, adalimumab was detected in the vascular compartment mainly at 214.8 mg/kg, and additionally in one male monkey at 82.9 mg/kg.

Most of the immunohistochemical changes observed in kidneys, spleen, and lungs were found to be reversible. However, the cellular diminution in the thymus in males was partially reversed, and did not reach the cellularity of the control animals after a 20-week recovery period. No adalimumab could be detected after the 20-week recovery period in the vessels of the organs and tissues examined.

Mutagenicity and Carcinogenicity

No carcinogenicity study was performed for adalimumab.

In vitro Genotoxicity

The mutagenic potential of adalimumab was tested in the Ames test and in the Escherichia coli reverse mutation assay. These tests are based on the ability of the test article to induce reverse mutations in selected loci of bacteria. Salmonella typhimurium strains TA 98, TA 100, TA 1535, and TA 1537, as well as Escherichia coli strain WP2 uvrA were used. Adalimumab (drug substance batch AF601-Ex pool) was tested at concentrations of 0, 20, 100, 500, 2500 and 5000 mcg/plate. Three plates were used per dose. Positive controls and a vehicle control (PBS buffer) were included in each experiment. Both the standard plate test (Ames test) and preincubation test with and without the addition of an exogenous metabolic activation system (S-9 fraction prepared from the livers of Aroclor 1254 treated rats) were performed. The results were considered positive if the revertant rate of a treatment group was at least twice that of the spontaneous revertant rate (vehicle control), a dose-response relationship occurred, and the experiments were reproducible.

No bacteriotoxic effect, such as reduced His- or Trp- background growth and decreased number of His+ or Trp+ revertants, were observed in adalimumab-treated plates when compared to the vehicle control. There was no increase in the number of mutant colonies under any experimental conditions in any strain of bacteria for the test article, whereas the positive controls showed the expected response when compared to the vehicle control. Therefore, the test substance is not mutagenic either in the Ames test or in the E. coli reverse mutation assays.

In vivo Genotoxicity

The potential clastogenic and spindle poison effects of adalimumab were tested in an in vivo micronucleus assay in NMRI mice after a single intravenous dose. The mice were randomly allocated into eight groups: two vehicle control groups (five mice/sex/group), four treatment groups (five mice/sex/group), and two positive control groups (five mice/group). The mice were intravenously treated once either with the vehicle control (PBS buffer); 224.5, 449.0, or 898 mg/kg (two groups) of adalimumab (drug substance batch AF601-Ex pool); or positive controls of 20 mg cyclophosphamide (two male and three female) or 0.15 mg/kg vincristine (three male and two female). All animals were sacrificed 24 hours after treatment except for one vehicle control group and one 898 mg/kg group, which were sacrificed 48 hours after dosing.

Bone marrow slides were prepared and stained with eosin and methylene solution, followed by Giemsa stain. The slides were examined microscopically for the following parameters: number of polychromatic erythrocytes (PCE), number of PCE containing micronuclei (MN), number of normochromatic erythrocytes (NCE), number of NCE containing MN, number of small micronuclei, and number of large micronuclei. The ratio of PCE to NCE was calculated. The results were considered positive if the following criteria were met: a dose-related and significant increase in the number of micronucleated PCE at the 24-hour and/or 48-hour intervals, and the proportion of cells containing micronuclei exceeded both the values of the concurrent negative control range and the negative historical control range.

The number of PCE and NCE containing MN in the adalimumab-treated groups was not significantly different from the concurrent, negative controls at any of the sacrificed intervals. However, the percentage of small MN in PCE in the cyclophosphamide-treated group and the percentage of large MN in PCE in the vincristine-treated group increased significantly as compared with the vehicle control. The ratio of PCE to NCE in all dose groups was always in the same range as that of the control values, suggesting normal erythropoiesis.

The results indicate that adalimumab does not have clastogenic activity or spindle poison effects. Also, no inhibition of erythropoiesis induced by the treatment with adalimumab was observed in NMRI mice.

Reproduction and Teratology

In pregnant monkeys adalimumab was distributed into the serum of the fetus and into the amnion fluid showing a distribution pattern that would be expected of a human IgG in a pregnant woman. No drug-related toxicity was observed. Distribution of adalimumab into the milk was not determined.

19 SUPPORTING PRODUCT MONOGRAPHS

1. HUMIRA® (adalimumab), Submission Control No: 225872, Product Monograph, AbbVie Corporation. June 25, 2019.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr **AMGEVITA**[®]

pronounced *am je vee' tah*

adalimumab injection

Single-Use Prefilled Syringe

Read this carefully before you start taking AMGEVITA and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about AMGEVITA.

AMGEVITA is a biosimilar biologic drug (biosimilar) to the reference biologic drug HUMIRA[®]. A biosimilar is authorized based on its similarity to a reference biologic drug already authorized for sale.

Serious Warnings and Precautions

Any medicine can have side effects. Like all medicines that affect your immune system, AMGEVITA can cause serious side effects. The possible serious side effects include:

- **Allergic reactions:** If you/your child develop a severe rash, swollen face or difficulty breathing while taking AMGEVITA call your doctor right away.
- **Hepatosplenic T-cell lymphoma:** Very rare reports of hepatosplenic T-cell lymphoma (HSTCL), a rare serious lymphoma that is often fatal, have been identified in patients treated with adalimumab. Most patients had also been treated with other medications for Crohn's disease and the majority were in adolescent and young adult males. The link between HSTCL and adalimumab is not clear.
- **Other cancer:** There have been very rare cases of certain kinds of cancer in patients taking adalimumab or other TNF-blockers. Some patients receiving adalimumab have developed types of cancer called non-melanoma skin cancer. Tell your doctor if you have a bump or open sore that does not heal. People with more serious rheumatoid arthritis that have had the disease for a long time may have a higher than average risk of getting a kind of cancer that affects the lymph system, called lymphoma. If you/your child take AMGEVITA or other TNF-blockers, your/your child's risk may increase. There have been cases of lymphoma and other cancers, including unusual types, in children, adolescents and young adults taking TNF-blocking agents, including adalimumab, which sometimes resulted in death. For children and adults taking TNF-blocker medicines, the chances of developing lymphoma or other cancers may increase.
- **Lupus-like symptoms:** Some patients have developed lupus-like symptoms that got better after their treatment was stopped. If you/your child have chest pains that do not go away, shortness of breath, joint pain or a rash on your cheeks or arms that gets worse in the sun, call your doctor right away. Your/your child's doctor may decide to stop your treatment.
- **Nervous system diseases:** There have been rare cases of disorders that affect the nervous system of people taking adalimumab or other TNF-blockers. Signs that you/your child could be experiencing a problem affecting your nervous system include: numbness or tingling, problems with your vision, weakness in your legs, and dizziness.

- **Serious infections:** There have been rare cases where patients taking adalimumab or other TNF-blocking agents have developed serious infections. Some of these cases have been life-threatening. Such infections include tuberculosis, infections caused by bacteria or fungi, and bacterial infections that have spread throughout the body (sepsis). Infection causes include tuberculosis, legionellosis (a serious form of bacterial pneumonia), listeriosis (an infection that usually develops after eating food contaminated by bacteria called listeria), and very rare cases of hepatitis B infection relapse.
- **Blood problems:** In some instances, patients treated with TNF-blocking agents may develop low blood counts, such as anemia (low red blood cells) or low platelets. If you/your child develop symptoms such as persistent fever, bleeding, or bruising, you should contact your/your child's doctor right away.

What is AMGEVITA used for?

AMGEVITA treatment should be started and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), adult and pediatric Crohn's disease (CD), ulcerative colitis (UC), adult and adolescent hidradenitis suppurativa (HS), psoriasis (Ps) or adult and pediatric uveitis, and familiar with the AMGEVITA efficacy and safety profile.

AMGEVITA is a medicine that is used in:

- adults with rheumatoid arthritis which is an inflammatory disease of the joints.
- patients 2 years of age and older who have polyarticular juvenile idiopathic arthritis.
- adults with psoriatic arthritis, which is an inflammatory disease of the joints and skin.
- adults with ankylosing spondylitis, which is a form of arthritis.
- adults with Crohn's disease, which is an inflammatory disease of the digestive tract.
- children 13 to 17 years weighing ≥ 40 kg who have severe Crohn's disease or who have Crohn's disease which has not responded to other usual treatments.
- adults with ulcerative colitis, which is an inflammatory disease of the bowel (colon).
- adults or adolescents (12 to 17 years of age, weighing ≥ 30 kg) with moderate to severe hidradenitis suppurativa (HS) who have not responded to antibiotics. HS is a painful, progressive, chronic inflammatory skin disease that causes nodules, abscesses, sinus tracts and fistulas under the breasts, underarms, buttocks and groin.
- adults with psoriasis, which is an inflammatory disease of the skin. Your doctor prescribed AMGEVITA to reduce the signs and symptoms of your plaque psoriasis.
- adults with uveitis, which is an inflammatory disease of the eye.
- Children with chronic non-infectious uveitis from 2 years of age with inflammation affecting the front of the eye.

Patients with rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, hidradenitis suppurativa, psoriasis, or uveitis may be given other medicines for their disease before they are given AMGEVITA. If you have ulcerative colitis or you/your child have Crohn's disease, you/your child will first be given other medicines. If you/your child do not respond well enough to these medicines, you/your child will be given AMGEVITA to reduce the signs and symptoms of your/your child's disease.

How does AMGEVITA work?

AMGEVITA is a fully human monoclonal antibody produced by cultured cells. Monoclonal antibodies are proteins that recognize and bind to other unique proteins. AMGEVITA binds to a specific protein called TNF-alpha (also known as tumour necrosis factor). People with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, or psoriasis have too much of TNF-alpha in their bodies. The extra TNF-alpha in your/your child's body can attack normal healthy body tissues and cause inflammation, especially in the tissues of your bones, cartilage, joints and digestive tract. By binding to TNF-alpha, AMGEVITA decreases the inflammation process of these diseases.

AMGEVITA helps reduce the signs and symptoms of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and psoriatic arthritis (such as pain and swollen joints), may help improve your/your child's ability to perform daily activities (such as getting dressed, walking and climbing stairs), and may help prevent further damage to your/your child's bones and joints. In addition, AMGEVITA helps reduce the signs and symptoms of ankylosing spondylitis (back pain and morning stiffness), and adult and pediatric Crohn's disease or ulcerative colitis (abdominal pain and diarrhea). AMGEVITA may also help normalize childhood growth and pubertal development, and improve the quality of life in children who have Crohn's disease (such as body image, functional and social skills, and emotional health). AMGEVITA may help improve the work productivity and activity impairment in caregivers of children with Crohn's disease.

AMGEVITA is also used to treat inflammatory lesions (nodules and abscesses) in adult and adolescents (12 to 17 years of age, weighing \geq 30 kg) with hidradenitis suppurativa.

AMGEVITA also helps reduce the signs and symptoms of psoriasis (such as pain, itching and scaly patches on skin).

AMGEVITA helps control uveitis by reducing the risk of inflammation and loss of vision in adult and pediatric patients.

AMGEVITA, however, can also lower your/your child's body's ability to fight infections. Taking AMGEVITA can make you/your child more prone to getting infections or make any infection you/your child have worse.

What are the ingredients in AMGEVITA?

The active substance is adalimumab.

- Each 0.8 mL prefilled syringe contains 40 mg of adalimumab (50 mg/mL) or 0.4 mL prefilled syringe contains 20 mg of adalimumab (50 mg/mL)

The other ingredients are glacial acetic acid, polysorbate 80, sodium hydroxide, sucrose and water for injection.

AMGEVITA comes in the following dosage forms:

AMGEVITA is available in the presentations listed below. Your/your child's doctor will prescribe the type that is best for you/your child.

- 40 mg/0.8 mL (50 mg/mL) or 20 mg/0.4 mL (50 mg/mL) single-use prefilled syringe
- 40 mg/0.8 mL (50 mg/mL) single-use prefilled autoinjector (SureClick®)

Do not use AMGEVITA if you/your child:

- have an allergy to any of the ingredients in AMGEVITA (see **What are the ingredients in AMGEVITA?** section). The needle cap of the prefilled syringe contains dry natural rubber, which is made from latex.
- have a serious infection such as tuberculosis, infections caused by bacteria or fungi, and bacterial infections that have spread throughout the body (sepsis).
- have moderate to severe heart failure (NYHA class III/IV).

To help avoid effects and ensure proper use, talk to your/your child's healthcare professional before you/your child take AMGEVITA. Talk about any health conditions or problems you/your child may have, including if you/your child:

- have or have had any kind of infection including an infection that is in only one place in your body (such as an open cut or sore), or an infection that is in your whole body (such as the flu). Having an infection could put you/your child at risk for serious side effects from AMGEVITA. If you are unsure, ask your/your child's doctor.
- have a history of infections that keep coming back or other conditions that might increase your/your child's risk of infections, including fungal infections.
- have ever had tuberculosis, or if you/your child have been in close contact with someone who has had tuberculosis. If you/your child develop any of the symptoms of tuberculosis (a dry cough that doesn't go away, weight loss, fever, night sweats) call your/your child's doctor right away. Your/your child's doctor will need to examine you/your child for tuberculosis and perform a skin test.
- resided or traveled to areas where there is a greater risk for certain kinds of infections such as tuberculosis, histoplasmosis, coccidioidomycosis, blastomycosis, or parasitic infections. These infections are caused by a bacteria or a fungus that can affect the lungs or other parts of your/your child's body. If you/your child take AMGEVITA these may become active or more severe. If you/your child don't know if you have lived in or travelled to an area where these infections are common, ask your/your child's doctor.
- have ever had liver injury or hepatitis B virus infection or are at risk of developing this infection. Signs and symptoms include the following: yellowing of the skin or eyes (jaundice), feeling of sickness, tiredness, loss of appetite, joint pain, fever, dark brown-coloured urine, vomiting, and abdominal pain. If you/your child experience any of these signs and symptoms, contact your/your child's doctor immediately. These symptoms may occur several months after starting therapy with AMGEVITA.
- experience any numbness or tingling or have ever had a disease that affects your nervous system like multiple sclerosis or Guillain-Barré syndrome.
- have or have had heart failure.
- are scheduled to have major surgery or dental procedures.
- are scheduled to be vaccinated for anything. It is recommended that pediatric Crohn's disease patients, if possible, be brought up to date with all immunizations according to current guidelines before starting AMGEVITA.

- are taking other medicines for your rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, psoriasis, or other conditions. You/your child can take other medicines provided your doctor has prescribed them or has told you it is acceptable to take them while you are taking AMGEVITA. It is important that you tell your/your child's doctor about any other medicines you/your child are taking for other conditions (for example, high blood pressure medicine) before you/your child start taking AMGEVITA.
- are taking other medicines for you/your child's Crohn's disease or other conditions. You/your child can take other medicines provided the doctor has prescribed them or has told you it is acceptable that you/your child takes them while he/she is taking AMGEVITA. It is important that you tell the doctor about any other medicines you/your child are taking for other conditions before you/your child start taking AMGEVITA.
- are taking any over-the-counter drugs, herbal medicines and vitamin and mineral supplements.
- are pregnant or could become pregnant.
- are breast-feeding or plan to breast-feed.
- are allergic to latex.

Other warnings you should know about:

Before starting, during and after treatment with AMGEVITA, you or your child should be checked for active or inactive tuberculosis infection with a tuberculin skin test.

If you/your child received AMGEVITA while pregnant, your/her baby may be at higher risk for getting an infection for up to approximately five months after the last dose of AMGEVITA received during pregnancy. It is important that your/her baby's doctors and other healthcare professionals know about your/her AMGEVITA use during pregnancy so they can decide when your/her baby should receive any vaccine.

Tell your healthcare professional about all the medications you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with AMGEVITA:

- other TNF-blockers such as Enbrel[®], Remicade[®], Cimzia[®], or Simponi[®]
- abatacept (Orenica[®])
- anakinra (Kineret[®])

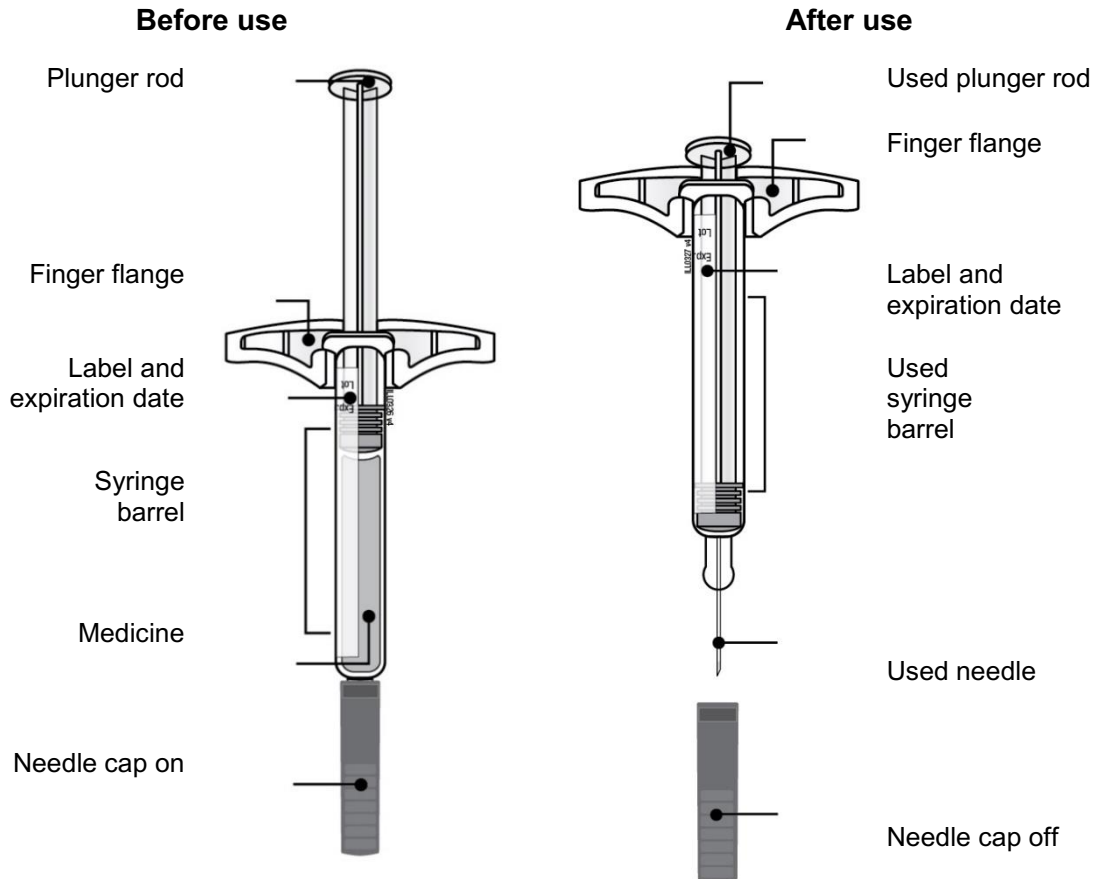
How to use AMGEVITA Single-use Prefilled Syringe:

AMGEVITA is administered by injection under the skin (by subcutaneous injection).

AMGEVITA Single-use Prefilled Syringe

The following instructions are for preparing and giving an injection of AMGEVITA using a single-use prefilled syringe.

Guide to parts



Important: Needle is inside

Important

Before you use a single-use AMGEVITA prefilled syringe, read this important information:

Storing your AMGEVITA prefilled syringe

- Keep the AMGEVITA prefilled syringe out of the reach of children.
- Keep the AMGEVITA prefilled syringe in the original carton to protect from light or physical damage.
- The AMGEVITA prefilled syringe should be kept in the refrigerator between 2°C to 8°C.

- If needed, you may store the AMGEVITA prefilled syringe at room temperature at 20°C to 25°C for up to 14 days. Throw away AMGEVITA that has been stored at room temperature after 14 days.
- **Do not** store the AMGEVITA prefilled syringe in extreme heat or cold. For example, avoid storing in your vehicle's glove box or trunk.
- **Do not** freeze.

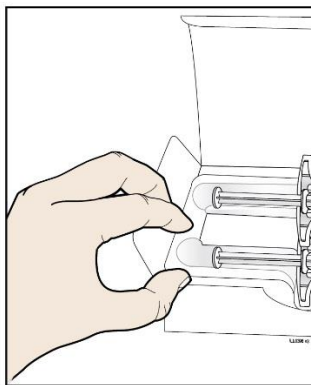
Using your AMGEVITA prefilled syringe

It is important that you do not try to give the injection unless you or your caregiver has received training from your healthcare provider.

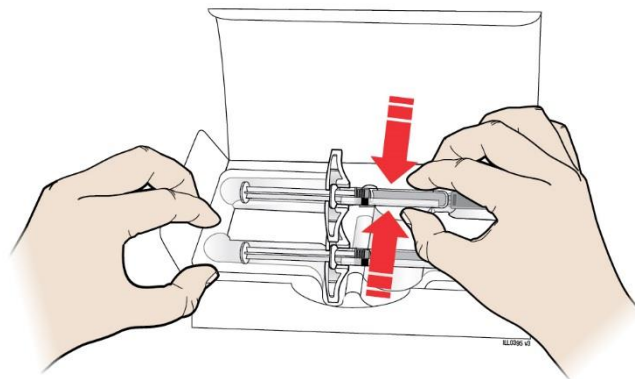
- **Do not** use an AMGEVITA prefilled syringe after the expiration date on the label.
- **Do not** shake the AMGEVITA prefilled syringe.
- **Do not** remove the needle cap from the AMGEVITA prefilled syringe until you are ready to inject.
- **Do not** use the AMGEVITA prefilled syringe if it has been frozen.
- **Do not** use the AMGEVITA prefilled syringe if it has been dropped on a hard surface. Part of the AMGEVITA prefilled syringe may be broken even if you cannot see the break. Use a new AMGEVITA prefilled syringe and call 1-866-502-6436.
- The needle cap of the prefilled syringe contains dry natural rubber, which is made from latex. Tell your doctor or pharmacist if you are allergic to latex.
- For more information or help, call 1-866-502-6436.

Step 1: Prepare

- A. Remove the number of AMGEVITA prefilled syringes you need from the package. Grab the syringe barrel to remove the syringe from the tray.



Place finger or thumb on edge of tray to secure it while you remove the syringe.



Grab Here

Put the original package with any unused syringes back in the refrigerator.

For safety reasons:

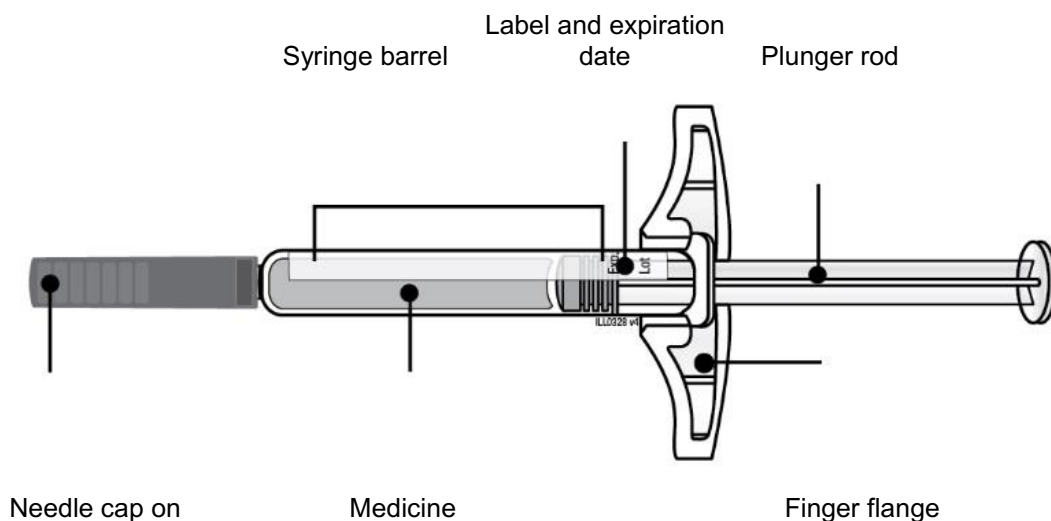
- **Do not** grasp the plunger rod.
- **Do not** grasp the needle cap.
- **Do not** remove the needle cap until you are ready to inject.
- **Do not** remove the finger flange. This is part of the syringe.

For a more comfortable injection, leave the prefilled syringe at room temperature for **15 to 30** minutes before injecting.

- **Do not** put the syringe back in the refrigerator once it has reached room temperature.
- **Do not** try to warm the syringe by using a heat source such as hot water or microwave.
- **Do not** leave the syringe in direct sunlight.
- **Do not** shake the syringe.

Important: Always hold the prefilled syringe by the syringe barrel.

B. Inspect the AMGEVITA prefilled syringe.



Always hold the syringe by the syringe barrel.

Make sure the medicine in the syringe is clear and colourless to slightly yellow.

Do not use the prefilled syringe if:

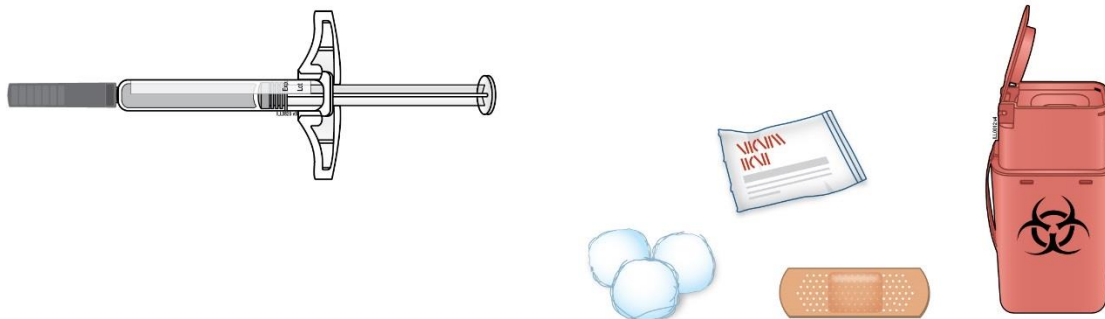
- the medicine is cloudy or discoloured, or contains flakes, or particles.
- any part appears cracked or broken.
- the needle cap is missing or not securely attached.
- the expiration date printed on the label has passed.

In any above cases, use a new prefilled syringe and call 1-866-502-6436.

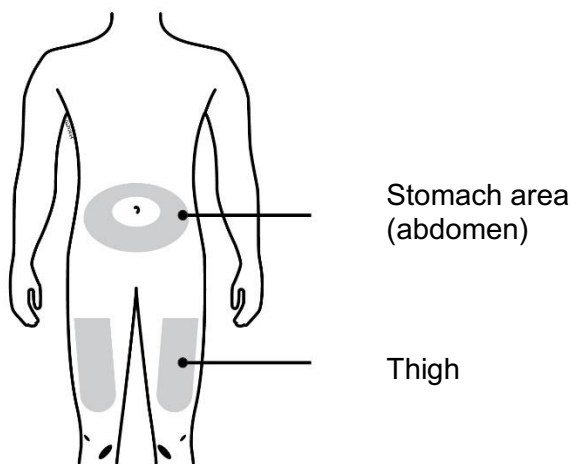
C. Gather all materials needed for your injection(s).

Wash your hands thoroughly with soap and water. On a clean, well-lit, flat work surface, place:

- New prefilled syringe(s)
- Alcohol wipes
- Cotton ball or gauze pad
- Adhesive bandage
- Sharps disposal container



D. Prepare and clean your injection site(s).



You can use:

- Your thigh
- Stomach area (abdomen), except for the **5 centimetre (2 inch)** area around the belly button.

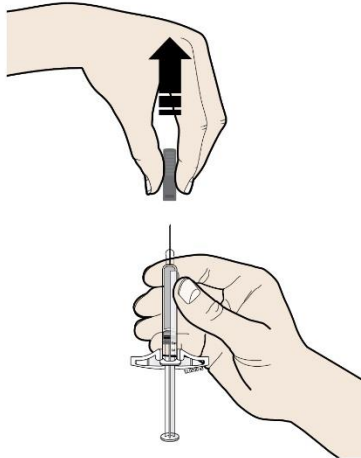
Clean the injection site with an alcohol wipe. Let your skin dry.

- **Do not** touch this area again before injecting.
- If you want to use the same injection site, make sure it is not the same spot on the injection site you used for a previous injection.
- **Do not** inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

- If you have psoriasis, you should avoid injecting directly into raised, thick, red, or scaly skin patch or lesion.

Step 2: Get ready

- E. Pull the needle cap straight out and away from your body when you are ready to inject.

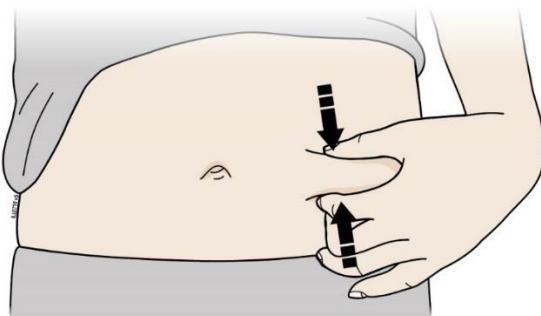


It is normal to see a drop of liquid at the end of the needle.

- **Do not** twist or bend the needle cap.
- **Do not** put the needle cap back onto the syringe.
- **Do not** remove the needle cap from the syringe until you are ready to inject.

Important: Throw the needle cap into the sharps disposal container provided.

- F. Pinch your injection site to create a firm surface.

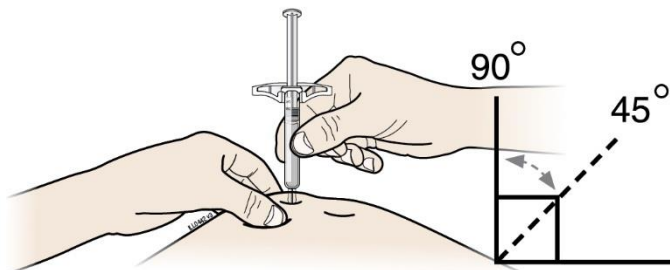


Pinch the skin firmly between your thumb and fingers, creating an area about **5 centimetres (2 inches)** wide.

Important: Keep skin pinched while injecting.

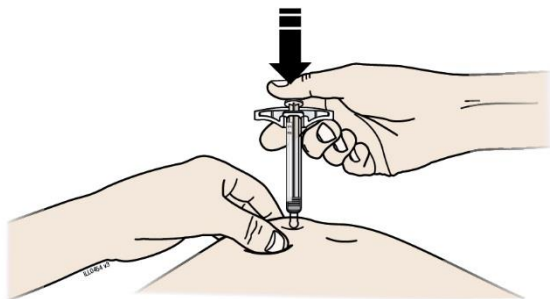
Step 3: Inject

- G. Hold the pinch. With the needle cap off, insert the syringe into your skin at 45 to 90 degrees.

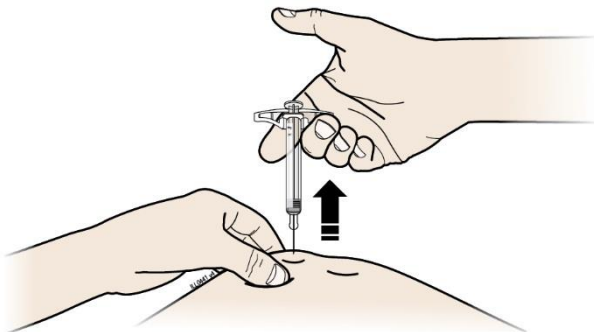


Do not place your finger on the plunger rod while inserting the needle.

- H. Using slow and constant pressure, **push** the plunger rod all the way down until it stops moving.



- I. When done, **release** your thumb, and gently lift the syringe off skin.



Step 4: Finish

J. Discard the used syringe and the needle cap in a sharps disposal container.



- Put the used syringe in a sharps disposal container immediately after use. **Do not** throw away (dispose of) the syringe in your household trash.
- Talk with your doctor or pharmacist about proper disposal. There may be local guidelines for disposal.
- If you do not have a sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak-resistant, and
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be provincial or local laws about how you should throw away used needles and syringes.
- **Important:** Always keep the syringe and the sharps disposal container out of the reach of children.
- **Do not** reuse the syringe.
- **Do not** use any medicine that is left in the used syringe.
- **Do not** recycle the syringe or the sharps disposal container or throw it into household trash.

K. Examine the injection site.

If there is blood, press a cotton ball or gauze pad on your injection site. **Do not** rub the injection site. Apply an adhesive bandage if needed.

Usual Dose:

Adults with Rheumatoid Arthritis, Psoriatic Arthritis or Ankylosing Spondylitis:

- The recommended dose is 40 mg administered every other week as a subcutaneous injection.

Patients, aged 2 years and older, with polyarticular juvenile idiopathic arthritis:

- Weighing 10 kg to less than 30 kg: The recommended dose of AMGEVITA is 20 mg every other week.
- Weighing 30 kg or more: The recommended dose of AMGEVITA is 40 mg every other week.

For patients who do not require a full 40 mg dose of AMGEVITA, a 20 mg pre-filled syringe is also available.

Adults with Crohn's Disease or Ulcerative Colitis:

- The recommended induction dose is 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days), followed by 80 mg at Week 2.
- The recommended maintenance dose regimen is 40 mg every other week beginning at Week 4.

Children, 13 to 17 years of age weighing \geq 40 kg, with Crohn's disease:

- The recommended dose is 160 mg initially at Week 0 (given as four 40 mg injections in one day, or as two 40 mg injections per day for two consecutive days), followed by 80 mg at Week 2 (given as two 40 mg injections). At Week 4, your child will begin a maintenance dose of 20 mg every other week. Depending on your child's response, the doctor may increase the dose to 40 mg every other week (given as one 40 mg injection).

For children who do not require a full 40 mg dose of AMGEVITA, a 20 mg pre-filled syringe is also available.

Adults with Hidradenitis Suppurativa:

- The recommended initial dose is 160 mg, followed by 80 mg two weeks later. The first dose of 160 mg can be administered as four injections in one day or as two injections per day for two consecutive days. The second dose of 80 mg is given as two 40 mg injections in one day.

The recommended maintenance dose regimen is 40 mg every week beginning four weeks after the initial dose

- Adolescents, 12 to 17 years of age weighing \geq 30 kg, with Hidradenitis Suppurativa:The recommended initial dose is 80 mg administered by subcutaneous injection, followed by 40 mg every other week starting one week later. Depending on your/your child's response, the doctor may increase the dose to 40 mg every week.

Adults with Psoriasis or Uveitis:

- The recommended dose is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose.

Children, from 2 years of age, with Uveitis:

- weighing less than 30 kg: the usual dose of AMGEVITA is 20 mg every other week with methotrexate. Your child's doctor may also prescribe an initial dose of 40 mg to be administered one week prior to the start of the usual dose if your child is older than 6 years of age.
- weighing 30 kg or more: the usual dose of AMGEVITA is 40 mg every other week with methotrexate. Your child's doctor may also prescribe an initial dose of 80 mg to be administered one week prior to the start of the usual dose.

For children who do not require a full 40 mg dose of AMGEVITA, a 20 mg pre-filled syringe is also available

Overdose:

If you think you/your child have used too much AMGEVITA, contact your/your child's healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to give yourself or your child an injection, you should inject the missed dose of AMGEVITA as soon as you remember. Then administer the next dose as you would have on the originally scheduled date.

What are possible side effects from using AMGEVITA:

These are not all the possible side effects you may feel when taking AMGEVITA. If you experience any side effects not listed here, contact your healthcare professional. Please also see **Warnings and Precautions**.

Tell your/your child's doctor immediately if you/your child experience any of the following:

- severe rash, hives or other signs of allergic reaction
- swollen face, hands, feet
- trouble breathing, swallowing
- sudden weight gain (this is possibly indicative of new or worsening heart failure)
- bruising or bleeding very easily, looking very pale; this could mean a blood problem such as low red blood cells (anemia) or low platelets.

Tell the doctor as soon as possible if you/your child notice any of the following:

- signs of infection such as fever, malaise, wounds, dental problems, burning on urination
- feeling weak or tired
- coughing
- tingling
- numbness
- double vision
- arm or leg weakness

- arm or leg pain, swelling or redness
- bump or open sore that does not heal
- red scaly patches or raised bumps that are filled with pus; this could be new or worsening hidradenitis suppurativa, new or worsening psoriasis or a skin infection
- alopecia (loss of hair)
- changes in the colour of the skin
- changes in the colour of your urine (dark or red)
- worsening of the appearance of a scar
- night sweats
- weight loss
- pain in the abdomen or chest

| Serious side effects and what to do about them | | | |
|---|--------------------------------------|----------------------------|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| VERY COMMON Injection site reaction | | ✓ | |
| COMMON Cough and cold symptoms, including sore throat Headache Rash Nausea Pneumonia Fever Abdominal pain | ✓ | ✓ ✓ ✓ ✓ ✓ ✓ | ✓ |
| UNCOMMON Tuberculosis Other serious infections Nerve disorders Appendicitis Blood clots: abdominal pain, chest pain, leg or arm pain with redness and swelling Bladder infection (painful urination) | | ✓ ✓ ✓ ✓ ✓ ✓ | ✓ ✓ ✓ ✓ ✓ ✓ |

| Serious side effects and what to do about them | | | |
|---|--------------------------------------|--------------|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| Hepatitis [jaundice (yellow skin, dark urine), abdominal pain, tiredness] | | ✓ | ✓ |

If you have troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on [Adverse Reaction Reporting](http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) (<http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C). Do not freeze.

Store in the original carton in order to protect from light.

A single AMGEVITA prefilled syringe may be stored at temperatures up to a maximum of 25°C for a period of up to 14 days. The prefilled syringe must be protected from light, and discarded if not used within the 14-day period.

Keep out of reach and sight of children.

If you want more information about AMGEVITA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#); the manufacturer's website www.amgen.ca, or by calling 1-866-502-6436.

This leaflet was prepared by Amgen Canada Inc.

Last Revised: November 4, 2020

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr **AMGEVITA**[®]

pronounced *am je vee' tah*

adalimumab injection

Single-Use Prefilled Sureclick[®] Autoinjector

Read this carefully before you start taking AMGEVITA and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about AMGEVITA.

AMGEVITA is a biosimilar biologic drug (biosimilar) to the reference biologic drug HUMIRA[®]. A biosimilar is authorized based on its similarity to a reference biologic drug already authorized for sale.

Serious Warnings and Precautions

Any medicine can have side effects. Like all medicines that affect your immune system, AMGEVITA can cause serious side effects. The possible serious side effects include:

- **Allergic reactions:** If you/your child develop a severe rash, swollen face or difficulty breathing while taking AMGEVITA call your doctor right away.
- **Hepatosplenic T-cell lymphoma:** Very rare reports of hepatosplenic T-cell lymphoma (HSTCL), a rare serious lymphoma that is often fatal, have been identified in patients treated with adalimumab. Most patients had also been treated with other medications for Crohn's disease and the majority were in adolescent and young adult males. The link between HSTCL and adalimumab is not clear.
- **Other cancer:** There have been very rare cases of certain kinds of cancer in patients taking adalimumab or other TNF-blockers. Some patients receiving adalimumab have developed types of cancer called non-melanoma skin cancer. Tell your doctor if you have a bump or open sore that does not heal. People with more serious rheumatoid arthritis that have had the disease for a long time may have a higher than average risk of getting a kind of cancer that affects the lymph system, called lymphoma. If you/your child take AMGEVITA or other TNF-blockers, your/your child's risk may increase. There have been cases of lymphoma and other cancers, including unusual types, in children, adolescents and young adults taking TNF-blocking agents, including adalimumab, which sometimes resulted in death. For children and adults taking TNF-blocker medicines, the chances of developing lymphoma or other cancers may increase.
- **Lupus-like symptoms:** Some patients have developed lupus-like symptoms that got better after their treatment was stopped. If you/your child have chest pains that do not go away, shortness of breath, joint pain or a rash on your cheeks or arms that gets worse in the sun, call your doctor right away. Your/your child's doctor may decide to stop your treatment.

- **Nervous system diseases:** There have been rare cases of disorders that affect the nervous system of people taking adalimumab or other TNF-blockers. Signs that you/your child could be experiencing a problem affecting your nervous system include: numbness or tingling, problems with your vision, weakness in your legs, and dizziness.
- **Serious infections:** There have been rare cases where patients taking adalimumab or other TNF-blocking agents have developed serious infections. Some of these cases have been life-threatening. Such infections include tuberculosis, infections caused by bacteria or fungi, and bacterial infections that have spread throughout the body (sepsis). Infection causes include tuberculosis, legionellosis (a serious form of bacterial pneumonia), listeriosis (an infection that usually develops after eating food contaminated by bacteria called listeria), and very rare cases of hepatitis B infection relapse.
- **Blood problems:** In some instances, patients treated with TNF-blocking agents may develop low blood counts, such as anemia (low red blood cells) or low platelets. If you/your child develop symptoms such as persistent fever, bleeding, or bruising, you should contact your/your child's doctor right away.

What is AMGEVITA used for?

AMGEVITA treatment should be started and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), adult and pediatric Crohn's disease (CD), ulcerative colitis (UC), adult and adolescent hidradenitis suppurativa (HS), psoriasis (Ps) or adult and pediatric uveitis, and familiar with the AMGEVITA efficacy and safety profile.

AMGEVITA is a medicine that is used in:

- adults with rheumatoid arthritis which is an inflammatory disease of the joints.
- patients 2 years of age and older who have polyarticular juvenile idiopathic arthritis.
- adults with psoriatic arthritis, which is an inflammatory disease of the joints and skin.
- adults with ankylosing spondylitis, which is a form of arthritis.
- adults with Crohn's disease, which is an inflammatory disease of the digestive tract.
- children 13 to 17 years weighing ≥ 40 kg who have severe Crohn's disease or who have Crohn's disease which has not responded to other usual treatments.
- adults with ulcerative colitis, which is an inflammatory disease of the bowel (colon).
- adults or adolescents (12 to 17 years of age, weighing ≥ 30 kg) with moderate to severe hidradenitis suppurativa (HS) who have not responded to antibiotics. HS is a painful, progressive, chronic inflammatory skin disease that causes nodules, abscesses, sinus tracts and fistulas under the breasts, underarms, buttocks and groin.
- adults with psoriasis, which is an inflammatory disease of the skin. Your doctor prescribed AMGEVITA to reduce the signs and symptoms of your plaque psoriasis.
- adults with uveitis, which is an inflammatory disease of the eye.
- Children with chronic non-infectious uveitis from 2 years of age with inflammation affecting the front of the eye.

Patients with rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, hidradenitis suppurativa, psoriasis, or uveitis may be given other medicines for their disease before they are given AMGEVITA. If you have ulcerative colitis or you/your child have Crohn's disease, you/your child will first be given other medicines. If you/your child do not respond well enough to these medicines, you/your child will be given AMGEVITA to reduce the signs and symptoms of your/your child's disease.

How does AMGEVITA work?

AMGEVITA is a fully human monoclonal antibody produced by cultured cells. Monoclonal antibodies are proteins that recognize and bind to other unique proteins. AMGEVITA binds to a specific protein called TNF-alpha (also known as tumour necrosis factor). People with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, or psoriasis have too much of TNF-alpha in their bodies. The extra TNF-alpha in your/your child's body can attack normal healthy body tissues and cause inflammation, especially in the tissues of your bones, cartilage, joints and digestive tract. By binding to TNF-alpha, AMGEVITA decreases the inflammation process of these diseases.

AMGEVITA helps reduce the signs and symptoms of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and psoriatic arthritis (such as pain and swollen joints), may help improve your/your child's ability to perform daily activities (such as getting dressed, walking and climbing stairs), and may help prevent further damage to your/your child's bones and joints. In addition, AMGEVITA helps reduce the signs and symptoms of ankylosing spondylitis (back pain and morning stiffness), and adult and pediatric Crohn's disease or ulcerative colitis (abdominal pain and diarrhea). AMGEVITA may also help normalize childhood growth and pubertal development, and improve the quality of life in children who have Crohn's disease (such as body image, functional and social skills, and emotional health). AMGEVITA may help improve the work productivity and activity impairment in caregivers of children with Crohn's disease.

AMGEVITA is also used to treat inflammatory lesions (nodules and abscesses) in adult and adolescents (12 to 17 years of age, weighing \geq 30 kg) with hidradenitis suppurativa.

AMGEVITA also helps reduce the signs and symptoms of psoriasis (such as pain, itching and scaly patches on skin).

AMGEVITA helps control uveitis by reducing the risk of inflammation and loss of vision in adult and pediatric patients.

AMGEVITA, however, can also lower your/your child's body's ability to fight infections. Taking AMGEVITA can make you/your child more prone to getting infections or make any infection you/your child have worse.

What are the ingredients in AMGEVITA?

The active substance is adalimumab.

- Each 0.8 mL prefilled SureClick® autoinjector contains 40 mg of adalimumab (50 mg/mL)

The other ingredients are glacial acetic acid, polysorbate 80, sodium hydroxide, sucrose and water for injection.

AMGEVITA comes in the following dosage forms:

AMGEVITA is available in the presentations listed below. Your/your child's doctor will prescribe the type that is best for you/your child.

- 40 mg/0.8 mL (50 mg/mL) single-use prefilled autoinjector (SureClick®)
- 20 mg/0.4 mL (50 mg/mL) or 40 mg/0.8 mL (50 mg/mL) single-use prefilled syringe

Do not use AMGEVITA if you/your child:

- have an allergy to any of the ingredients in AMGEVITA (see **What are the ingredients in AMGEVITA?** section). The yellow cap on the AMGEVITA SureClick® autoinjector contains a needle cover that is composed of dry natural rubber, which is made from latex.
- have a serious infection such as tuberculosis, infections caused by bacteria or fungi, and bacterial infections that have spread throughout the body (sepsis).
- child have moderate to severe heart failure (NYHA class III/IV).

To help avoid effects and ensure proper use, talk to your/your child's healthcare professional before you/your child take AMGEVITA. Talk about any health conditions or problems you/your child may have, including if you/your child:

- have or have had any kind of infection including an infection that is in only one place in your body (such as an open cut or sore), or an infection that is in your whole body (such as the flu). Having an infection could put you/your child at risk for serious side effects from AMGEVITA. If you are unsure, ask your/your child's doctor.
- have a history of infections that keep coming back or other conditions that might increase your/your child's risk of infections, including fungal infections.
- have ever had tuberculosis, or if you/your child have been in close contact with someone who has had tuberculosis. If you/your child develop any of the symptoms of tuberculosis (a dry cough that doesn't go away, weight loss, fever, night sweats) call your/your child's doctor right away. Your/your child's doctor will need to examine you/your child for tuberculosis and perform a skin test.
- resided or traveled to areas where there is a greater risk for certain kinds of infections such as tuberculosis, histoplasmosis, coccidioidomycosis, blastomycosis, or parasitic infections. These infections are caused by a bacteria or a fungus that can affect the lungs or other parts of your/your child's body. If you/your child take AMGEVITA these may become active or more severe. If you/your child don't know if you have lived in or travelled to an area where these infections are common, ask your/your child's doctor.
- have ever had liver injury or hepatitis B virus infection or are a risk of developing this infection. Signs and symptoms include the following: yellowing of the skin or eyes (jaundice), feeling of sickness, tiredness, loss of appetite, joint pain, fever, dark brown-coloured urine, vomiting, and abdominal pain. If you/your child experience any of these signs and symptoms, contact your/your child's doctor immediately. These symptoms may occur several months after starting therapy with AMGEVITA.
- experience any numbness or tingling or have ever had a disease that affects your nervous system like multiple sclerosis or Guillain-Barré syndrome.
- have or have had heart failure.

- are scheduled to have major surgery or dental procedures.
- are scheduled to be vaccinated for anything. It is recommended that pediatric Crohn's disease patients, if possible, be brought up to date with all immunizations according to current guidelines before starting AMGEVITA.
- are taking other medicines for your rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, psoriasis, or other conditions. You/your child can take other medicines provided your doctor has prescribed them or has told you it is acceptable to take them while you are taking AMGEVITA. It is important that you tell your/your child's doctor about any other medicines you/your child are taking for other conditions (for example, high blood pressure medicine) before you/your child start taking AMGEVITA.
- are taking other medicines for you/your child's Crohn's disease or other conditions. You/your child can take other medicines provided the doctor has prescribed them or has told you it is acceptable that you/your child takes them while he/she is taking AMGEVITA. It is important that you tell the doctor about any other medicines you/your child is taking for other conditions before you/your child starts taking AMGEVITA.
- are taking any over-the-counter drugs, herbal medicines and vitamin and mineral supplements.
- are pregnant or could become pregnant.
- are breast-feeding or plan to breast-feed.
- are allergic to latex.

Other warnings you should know about:

Before starting, during and after treatment with AMGEVITA, you or your child should be checked for active or inactive tuberculosis infection with a tuberculin skin test.

If you/your child received AMGEVITA while pregnant, your/her baby may be at higher risk for getting an infection for up to approximately five months after the last dose of AMGEVITA received during pregnancy. It is important that your/her baby's doctors and other healthcare professionals know about your/her AMGEVITA use during pregnancy so they can decide when your/her baby should receive any vaccine.

Tell your healthcare professional about all the medications you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with AMGEVITA:

- other TNF-blockers such as Enbrel[®], Remicade[®], Cimzia[®], or Simponi[®]
- abatacept (Orenica[®])
- anakinra (Kineret[®])

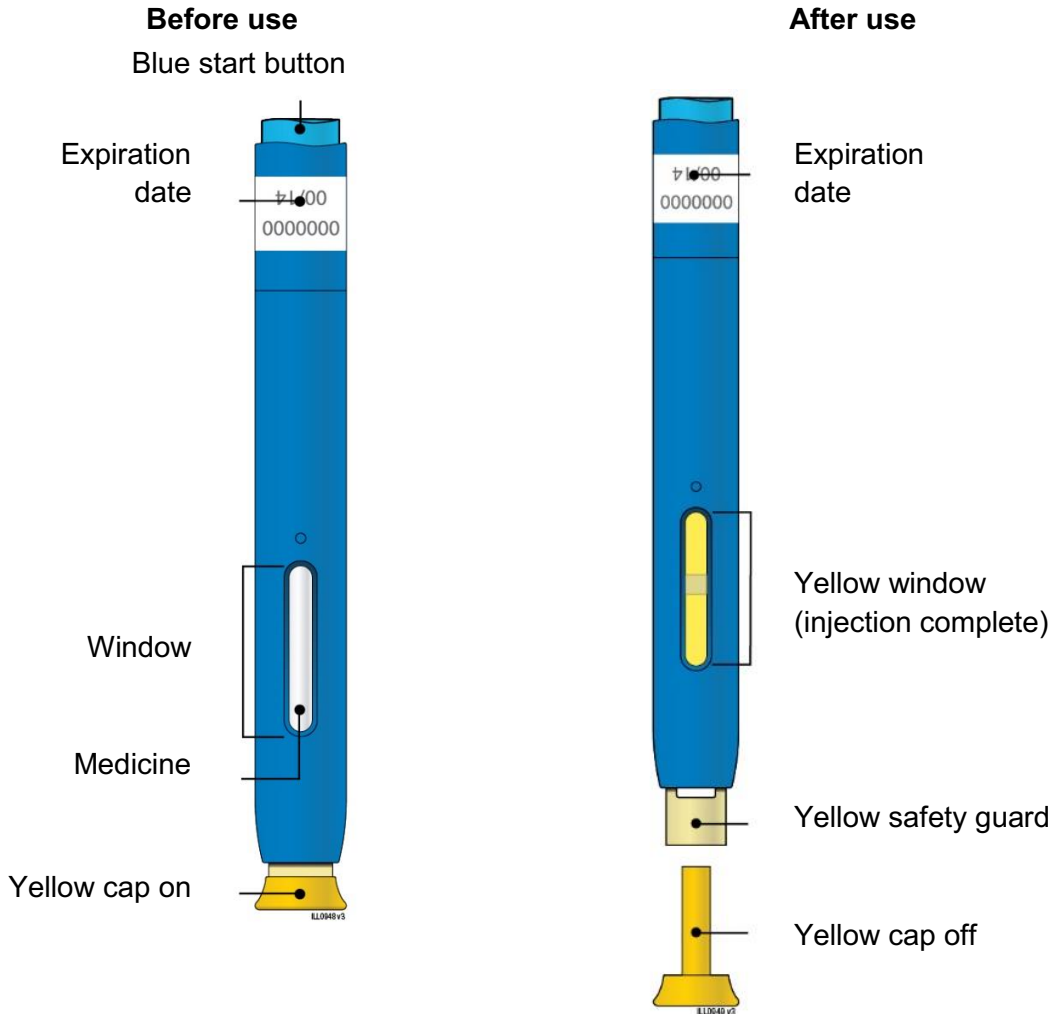
How to use AMGEVITA:

AMGEVITA is given as an injection under the skin (subcutaneous or SC).

AMGEVITA Single-use Prefilled SureClick® Autoinjector

The following instructions are for preparing and giving an injection of AMGEVITA using a single-use prefilled SureClick® autoinjector.

Guide to parts



Important: Needle is inside

Important:

Before you use an AMGEVITA SureClick® autoinjector, read this important information:

Storing your AMGEVITA SureClick® autoinjector

- Keep the AMGEVITA SureClick® autoinjector out of the reach of children.
- Keep the AMGEVITA SureClick® autoinjector in the original carton to protect from light or physical damage.
- The AMGEVITA SureClick® autoinjector should be kept in the refrigerator (2°C to 8°C).
- If needed, you may store the AMGEVITA SureClick® autoinjector at room temperature at 20°C to 25°C for up to 14 days. Throw away AMGEVITA that has been stored at room temperature after 14 days.
- **Do not** store the AMGEVITA SureClick® autoinjector in extreme heat or cold. For example, avoid storing in your vehicle's glove box or trunk.
- **Do not** freeze.

Using your AMGEVITA SureClick® autoinjector

It is important that you do not try to give the injection unless you or your caregiver has received training from your healthcare provider.

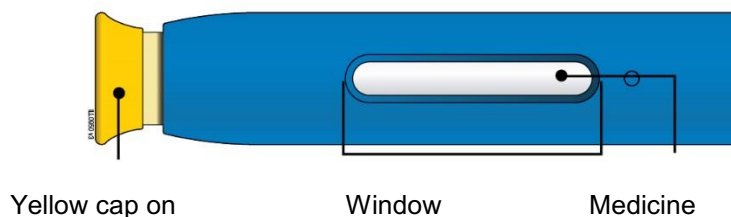
- **Do not** use an AMGEVITA SureClick® autoinjector after the expiration date on the label.
- **Do not** shake the AMGEVITA SureClick® autoinjector.
- **Do not** remove the yellow cap from the AMGEVITA SureClick® autoinjector until you are ready to inject.
- **Do not** use the AMGEVITA SureClick® autoinjector if it has been frozen.
- **Do not** use an AMGEVITA SureClick® autoinjector if it has been dropped on a hard surface. Part of the AMGEVITA SureClick® autoinjector may be broken even if you cannot see the break. Use a new AMGEVITA SureClick® autoinjector.
- The yellow cap on the AMGEVITA SureClick® autoinjector contains a needle cover that is composed of dry natural rubber, which is made from latex. Tell your healthcare provider if you are allergic to latex.
- For more information or help call 1-866-502-6436.

Step 1: Prepare

A. Remove one AMGEVITA SureClick® autoinjector from the package.

1. Carefully lift the autoinjector straight up out of the box.
2. Put the original package with any unused autoinjectors back in the refrigerator.
3. For a more comfortable injection, leave the autoinjector at room temperature for **15 to 30** minutes before injecting.
 - **Do not** put the autoinjector back in the refrigerator once it has reached room temperature.
 - **Do not** try to warm the autoinjector by using a heat source such as hot water or microwave
 - **Do not** shake the autoinjector
 - **Do not** remove the yellow cap from the autoinjector yet

B. Inspect the AMGEVITA SureClick® autoinjector.



Make sure the medicine in the window is clear and colourless to slightly yellow.

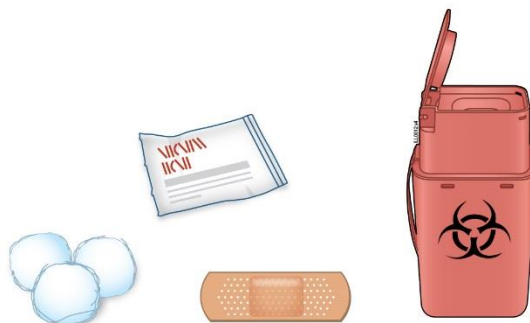
- **Do not** use autoinjector if:
 - the medicine is cloudy or discoloured, or contains flakes, or particles
 - any part appears cracked or broken
 - the autoinjector has been dropped
 - the yellow cap is missing or not securely attached
 - the expiration date printed on the label has passed.

In all cases, use a new autoinjector, and call 1-866-502-6436.

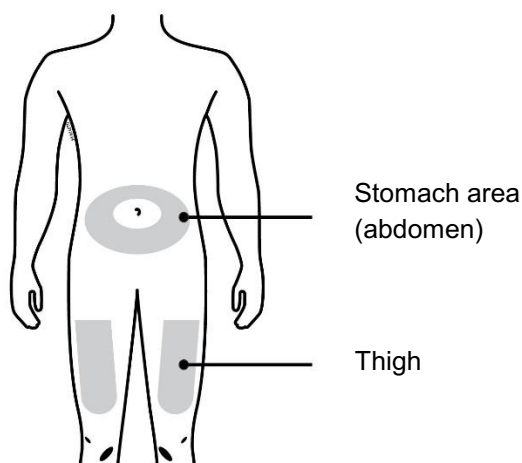
C. Gather all materials needed for your injection.

Wash your hands thoroughly with soap and water. On a clean, well-lit work surface, place the:

- New autoinjector
- Alcohol wipes
- Cotton ball or gauze pad
- Adhesive bandage
- Sharps disposal container



D. Prepare and clean your injection site.



You can use:

- Your thigh
- Stomach area (abdomen), except for a 5 centimetre (2-inch) area around your navel.

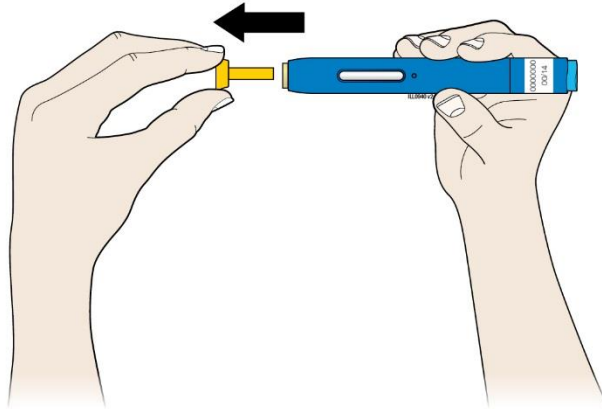
Clean the injection site with an alcohol wipe. Let your skin dry.

- **Do not** touch this area again before injecting.
- If you want to use the same injection site, make sure it is not the same spot on the injection site you used for a previous injection.
- **Do not** inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

- If you have psoriasis, you should avoid injecting directly into raised, thick, red, or scaly skin patch or lesion.

Step 2: Get ready

- E. Pull the yellow cap straight off when you are ready to inject.

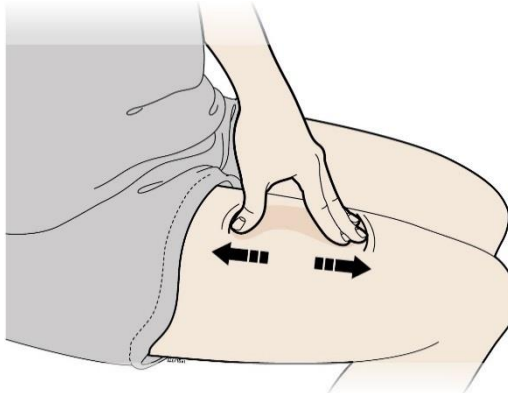


It is normal to see a drop of liquid at the end of the needle or yellow safety guard.

- **Do not** twist or bend the yellow cap.
- **Do not** put the yellow cap back onto the autoinjector.
- **Do not** remove the yellow cap from the autoinjector until you are ready to inject.

- F. Stretch or pinch your injection site to create a firm surface.

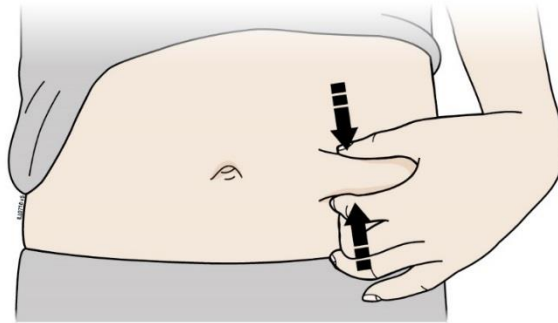
Stretch method



Stretch skin firmly by moving your thumb and fingers in opposite directions, creating an area about **5** centimetres (**2** inches) wide.

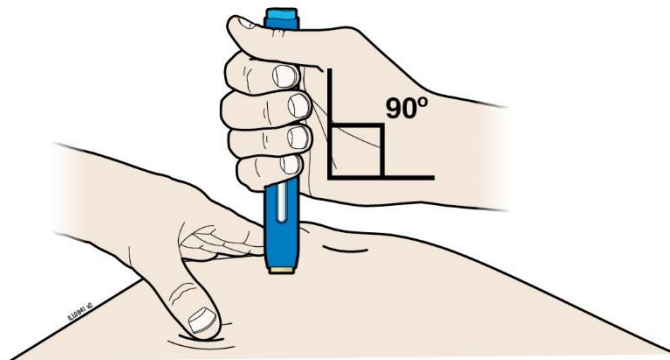
OR

Pinch method



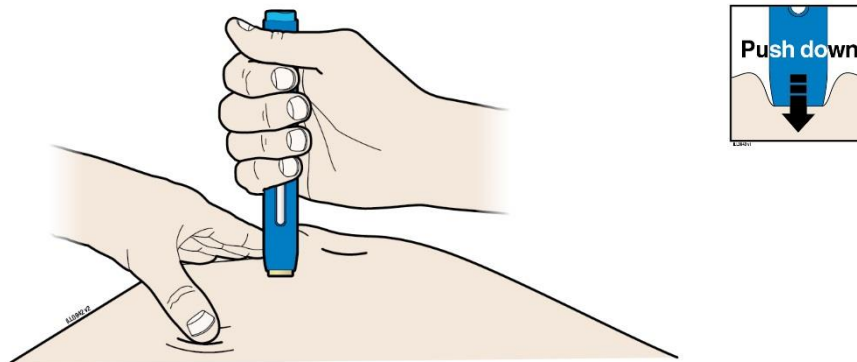
Step 3: Inject

- G. Hold the stretch or pinch. With the yellow cap off, **place** autoinjector on skin at 90 degrees.



Important: Do not touch the blue start button yet.

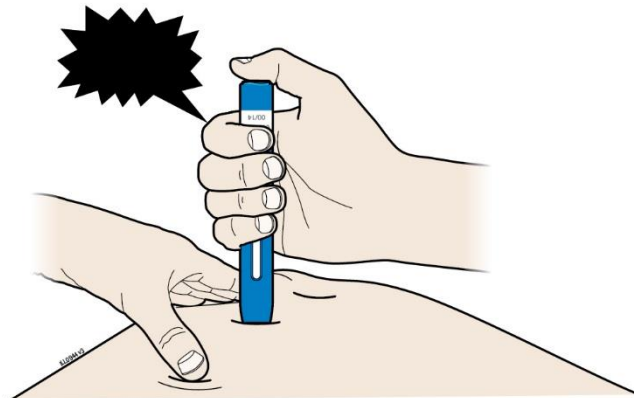
- H. Firmly **push** the autoinjector onto skin until it stops moving.



Important: You must push all the way down but **do not** touch blue start button until you are ready to inject.

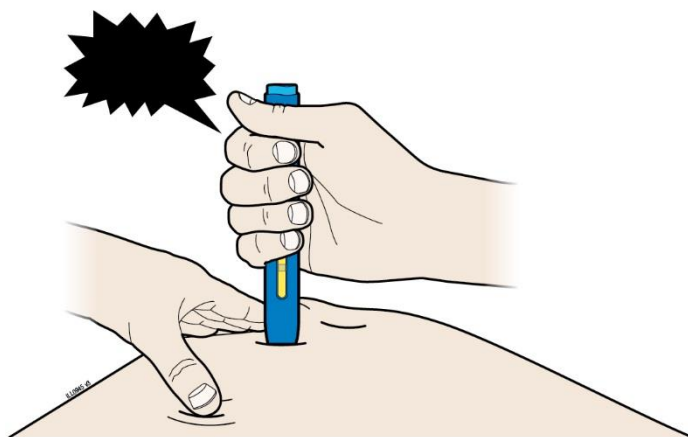
I. When you are ready to inject, **press** the blue start button.

“Click”

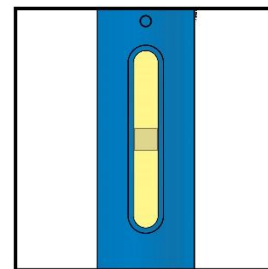


J. Keep **pushing** down on your skin. Your injection could take about 10 seconds.

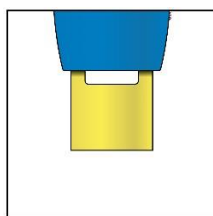
“Click”



~10s



Window turns yellow when injection is done

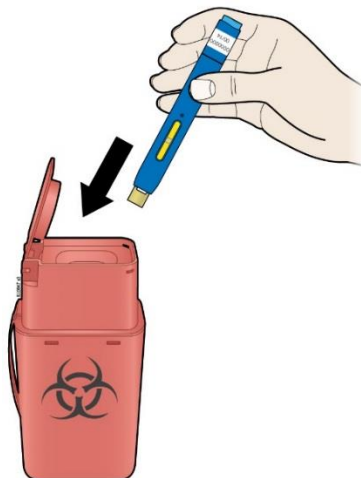


NOTE: After you remove autoinjector from your skin, the needle will be automatically covered.

Important: When you remove the autoinjector, if the window has not turned yellow, or if it looks like the medicine is still injecting, this means you have not received a full dose. Call your healthcare provider immediately.

Step 4: Finish

- K. Discard the used autoinjector and the yellow cap.



- Put the used SureClick® Autoinjector in a sharps disposal container right away after use. Do not throw away (dispose of) the SureClick® Autoinjector in your household trash.
 - If you do not have a sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak-resistant, and
 - properly labeled to warn of hazardous waste inside the container.
 - When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be provincial or local laws about how you should throw away used needles and syringes.
 - **Important:** Always keep the autoinjector and the sharps disposal container out of the reach of children.
 - **Do not** reuse the autoinjector.
 - **Do not** recycle the autoinjector or sharps disposal container or throw them into household trash.
- L. Examine the injection site.
- If there is blood, press a cotton ball or gauze pad on your injection site. **Do not** rub the injection site. Apply an adhesive bandage if needed.

Commonly asked questions

What will happen if I press the blue start button before I am ready to do the injection on my skin?

Even when you press the blue start button, the injection will only happen when the yellow safety guard is also pushed into the autoinjector.

Can I move the autoinjector around on my skin while I am choosing an injection site?

It is okay to move the autoinjector around on the injection site as long as you **do not** press the blue start button. However, if you press the blue start button and the yellow safety guard is pushed into the autoinjector, the injection will begin.

Can I release the blue start button after I start my injection?

You can release the blue start button, but continue to hold the autoinjector firmly against your skin during the injection.

Will the blue start button pop up after I release my thumb?

The blue start button may not pop up after you release your thumb if you held your thumb down during the injection. This is okay.

What do I do if I didn't hear a click after pushing the device down on my skin for 10 seconds?

If you didn't hear a click, you can confirm a complete injection by checking that the window has turned yellow.

Whom do I contact if I need help with the autoinjector or my injection?

If you have any questions about the autoinjector, its storage, or about your injection call 1-866-502-6436 for help.

Usual Dose:

Adults with Rheumatoid Arthritis, Psoriatic Arthritis or Ankylosing Spondylitis:

- The recommended dose is 40 mg administered every other week as a subcutaneous injection.

Patients, aged 2 years and older, with polyarticular juvenile idiopathic arthritis:

- Weighing 10 kg to less than 30 kg: The recommended dose of AMGEVITA is 20 mg every other week.
- Weighing 30 kg or more: The recommended dose of AMGEVITA is 40 mg every other week.

For patients who do not require a full 40 mg dose of AMGEVITA, a 20 mg pre-filled syringe is also available.

Adults with Crohn's Disease or Ulcerative Colitis:

- The recommended induction dose is 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days), followed by 80 mg at Week 2.
- The recommended maintenance dose regimen is 40 mg every other week beginning at Week 4.

Children, 13 to 17 years of age weighing \geq 40 kg, with Crohn's disease:

- The recommended dose is 160 mg initially at Week 0 (given as four 40 mg injections in one day, or as two 40 mg injections per day for two consecutive days), followed by 80 mg at Week 2 (given as two 40 mg injections). At Week 4, your child will begin a maintenance

dose of 20 mg every other week. Depending on your child's response, the doctor may increase the dose to 40 mg every other week (given as one 40 mg injection).

For children who do not require a full 40 mg dose of AMGEVITA, a 20 mg pre-filled syringe is also available.

Adults with Hidradenitis Suppurativa:

- The recommended initial dose is 160 mg, followed by 80 mg two weeks later. The first dose of 160 mg can be administered as four injections in one day or as two injections per day for two consecutive days. The second dose of 80 mg is given as two 40 mg injections in one day.
- The recommended maintenance dose regimen is 40 mg every week beginning four weeks after the initial dose.

Adolescents, 12 to 17 years of age weighing \geq 30 kg, with Hidradenitis Suppurativa:

- The recommended initial dose is 80 mg administered by subcutaneous injection, followed by 40 mg every other week starting one week later. Depending on your/your child's response, the doctor may increase the dose to 40 mg every week.

Adults with Psoriasis or Uveitis:

- The recommended dose is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose.

Children, from 2 years of age, with Uveitis:

- weighing less than 30 kg: the usual dose of AMGEVITA is 20 mg every other week with methotrexate. Your child's doctor may also prescribe an initial dose of 40 mg to be administered one week prior to the start of the usual dose if your child is older than 6 years of age.
- weighing 30 kg or more: the usual dose of AMGEVITA is 40 mg every other week with methotrexate. Your child's doctor may also prescribe an initial dose of 80 mg to be administered one week prior to the start of the usual dose.

For children who do not require a full 40 mg dose of AMGEVITA, a 20 mg pre-filled syringe is also available

Overdose:

| |
|--|
| If you think you/your child have taken too much AMGEVITA, contact your/your child's healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms. |
|--|

Missed Dose:

If you forget to give yourself or your child an injection, you should inject the missed dose of AMGEVITA as soon as you remember. Then administer the next dose as you would have on the originally scheduled date.

What are possible side effects from using AMGEVITA:

These are not all the possible side effects you may feel when taking AMGEVITA. If you experience any side effects not listed here, contact your healthcare professional. Please also see **Warnings and Precautions**.

Tell your/your child's doctor immediately if you/your child experience any of the following:

- severe rash, hives or other signs of allergic reaction
- swollen face, hands, feet
- trouble breathing, swallowing
- sudden weight gain (this is possibly indicative of new or worsening heart failure)
- bruising or bleeding very easily, looking very pale; this could mean a blood problem such as low red blood cells (anemia) or low platelets.

Tell the doctor as soon as possible if you/your child notice any of the following:

- signs of infection such as fever, malaise, wounds, dental problems, burning on urination
- feeling weak or tired
- coughing
- tingling
- numbness
- double vision
- arm or leg weakness
- arm or leg pain, swelling or redness
- bump or open sore that does not heal
- red scaly patches or raised bumps that are filled with pus; this could be new or worsening hidradenitis suppurativa, new or worsening psoriasis or a skin infection
- alopecia (loss of hair)
- changes in the colour of the skin
- changes in the colour of your urine (dark or red)
- worsening of the appearance of a scar
- night sweats
- weight loss
- pain in the abdomen or chest

| Serious side effects and what to do about them | | | |
|--|--------------------------------------|---------------------------|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| VERY COMMON Injection site reaction | | ✓ | |
| COMMON Cough and cold symptoms, including sore throat Headache Rash Nausea Pneumonia Fever Abdominal pain | ✓ ✓ | ✓ ✓ ✓ ✓ ✓ | ✓ |
| UNCOMMON Tuberculosis Other serious infections Nerve disorders Appendicitis | | ✓ ✓ ✓ ✓ | ✓ ✓ ✓ ✓ |
| Blood clots: abdominal pain, chest pain, leg or arm pain with redness and swelling Bladder infection (painful urination) Hepatitis [jaundice (yellow skin, dark urine), abdominal pain, tiredness] | | ✓ ✓ ✓ | ✓ ✓ ✓ |

If you have troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on [Adverse Reaction Reporting](http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) (<http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C). Do not freeze.

Store in the original carton in order to protect from light.

A single-use AMGEVITA prefilled SureClick® autoinjector may be stored at temperatures up to a maximum of 25°C for a period of up to 14 days. The prefilled SureClick® autoinjector must be protected from light, and discarded if not used within the 14-day period.

Keep out of reach and sight of children.

If you want more information about AMGEVITA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#); the manufacturer's website www.amgen.ca, or by calling 1-866-502-6436.

This leaflet was prepared by Amgen Canada Inc.

Last Revised: November 04, 2020